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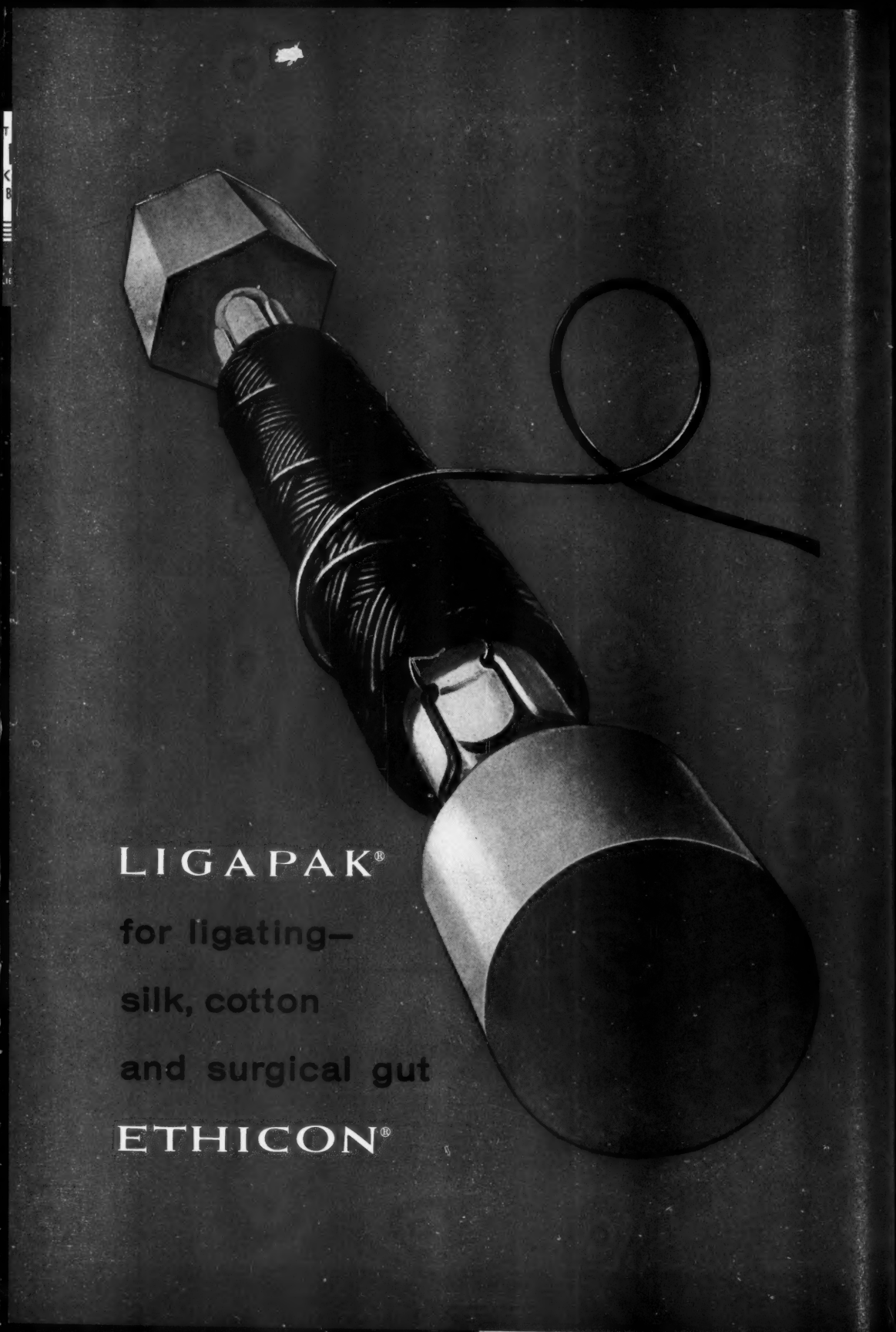
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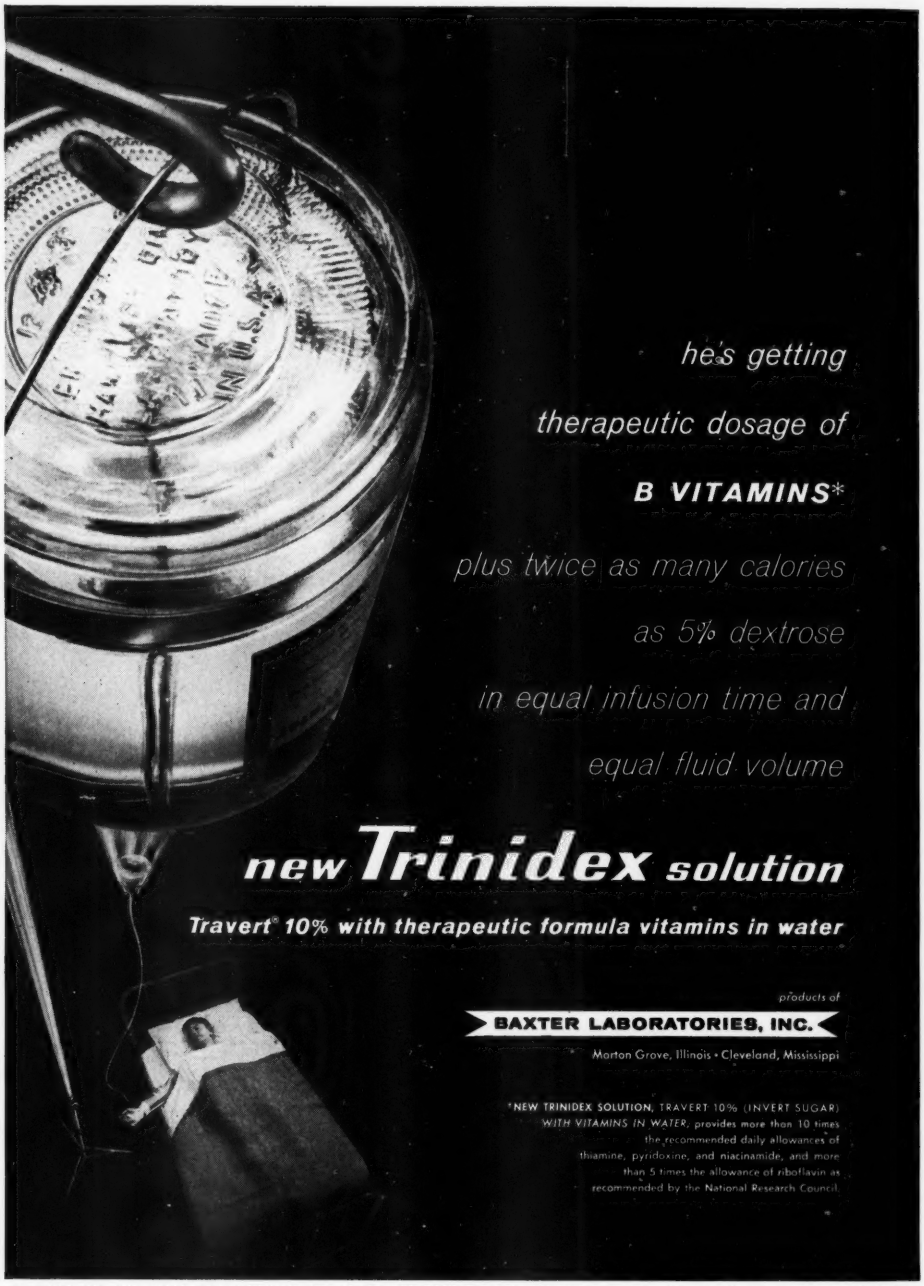
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A STUDY OF THE SERUM AMYLASE CONCENTRATION IN PATIENTS WITH ACUTE PERFORATION OF GASTRODUODENAL ULCERS

J. HERMAN MAHAFFEY, M.D., H. LEROY BROCKMAN, M.D.,
GEORGE L. JORDAN, JR., M.D., F.A.C.S., and JOHN M. HOWARD, M.D., Houston, Texas

THE VALUE of the serum amylase determination in the diagnosis of acute pancreatitis is universally recognized, for the use of this test has resulted in an increase in the frequency with which this disease is diagnosed. There are, however, other acute intra-abdominal diseases which may produce, perhaps indirectly, an elevation of the serum amylase concentration. These include perforations of the upper gastrointestinal tract, acute cholecystitis, common duct stone, strangulated intestinal obstruction, and appendiceal peritonitis.

Several investigators have reported patients with acute perforation of gastroduodenal ulcers in whom there were elevations in the serum amylase concentration to levels previously thought to be diagnostic of pancreatitis. Such a finding carries considerable diagnostic importance as an acute perforation of a peptic ulcer is one of the disease processes most likely to be confused with acute pancreatitis. That they be accurately differentiated is essential, as operative intervention is indicated for the former while most patients with the latter disease are treated nonoperatively. An error in diagnosis based upon a misinterpretation of this test has probably led to at least 1 death. Probstein reported an elevated serum amylase concentration in 4 of 17 patients with an acute perforated peptic ulcer. Three of these patients were treated surgically. The condition of the fourth patient was incorrectly diagnosed as acute pancreatitis and operation was deferred. The patient expired and necrospy revealed only a perforated gastric ulcer contiguous with but not penetrating the pancreas. Hughes noted an elevation of the urinary amylase in 4 of 40 patients with an anterior perforation of a duodenal ulcer. Three of these patients had fat necrosis seen at the time of surgery, though the pancreas appeared normal. The fourth patient had neither fat necrosis nor gross abnormality of the pancreas. Wapshaw in a study of 30 pa-

From the Department of Surgery, Baylor University College of Medicine, and the Jefferson Davis and Veterans Administration Hospitals, Houston, Texas.
Supported in part by the Cora and Webb Mading Fund for Surgical Research.

tients, stated that elevations in the serum amylase concentration were noted only when the time lapse between perforation and amylase determination was greater than 6 hours. Four of his 15 patients, studied 7 to 12 hours postperforation, and 2 of the 3, seen 15 to 24 hours postperforation, had significant elevations. Musgrove noted a direct relationship between the size of the perforation, the degree of peritoneal soilage, and the serum amylase concentration in 8 patients studied.

The purpose of the present study was to extend the investigation of the incidence and significance of elevated serum amylase concentrations following acute anterior perforations of gastroduodenal ulcers.

MATERIALS AND METHODS

This is a study of 51 surgical patients with acute perforations of gastroduodenal or marginal ulcers on whom the serum amylase concentration was determined preoperatively. In each instance the test was performed immediately after the patient reached the hospital and prior to the administration of narcotics. Amylase determinations were done by the method of Wohlgemuth, as described by Bray. In a series of 70 controls in this laboratory, the normal range was 15 to 50 units.

RESULTS

Eight patients (15.7 per cent) had a distinct elevation of the serum amylase concentration. Three additional patients had values of 52, 53, and 53 respectively, but small deviations from normal are not of clinical significance. Only 1 (4.5 per cent) of the 22 patients admitted less than 6 hours following perforation had an elevated serum amylase concentration (Fig. 1). The most significant elevations were seen when the perforation had occurred 12 or more hours prior to admission. Twenty-six per cent of the 19 patients seen late after perforation had significant elevations ranging from 94 to 220 units.

The size of the perforation was recorded in 30 instances (Fig. 2). Only 2 (7.4 per cent) patients in whom the perforation was less than 1 centimeter in diameter demonstrated an elevation. However, there was a distinct elevation in all 3 patients in whom the diameter of the perforation was greater than 1 centimeter.

An estimation of the amount of fluid in the peritoneal cavity was recorded in 39 instances (Fig. 3). Only 1 (5.3 per cent) of the 19 patients in whom the degree of intraperitoneal spillage of gastroduodenal contents was estimated by the surgeon to be less than 600 milliliters had an elevated amylase, whereas 30.0 per cent of the 20 patients with a spillage of greater degree demonstrated a significant rise.

A definite record of the time of the last meal or alcoholic intake prior to perforation was recorded in 16 patients. The amylase concentration was elevated only in the patients who had ingested food or alcohol within 3 hours prior to perforation (Fig. 4).

DISCUSSION

Although the pancreas was seldom specifically explored in this study, pancreatic inflammation was not observed. Our findings corroborate those of previous investigators in that the size of the perforation, the degree of spillage into the peritoneal cavity, the interval elapsing following a meal, and the interval between perforation and determination of the enzyme concentration appeared to be related to the serum amylase concentration.

In this study the highest serum amylase concentrations were recorded when the test was performed more than 12 hours after perforation. This is in contrast to findings in acute pancreatitis in which the elevation is often observed sooner. This diagnostic distinction is not reliable, however, as one occasionally sees a late rise in the amylase concentration in patients with acute pancreatitis. Furthermore, one of our patients with an acute perforation demonstrated a rise within 6 hours. Consequently, the serum amylase concentration cannot be relied upon for absolute differentiation of these two

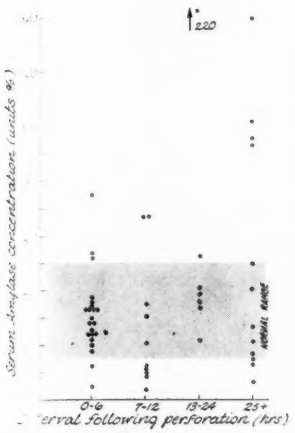


FIG. 1.

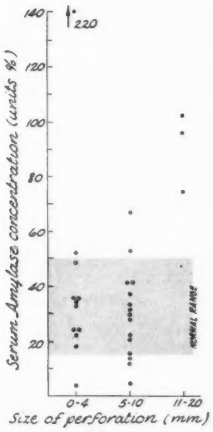
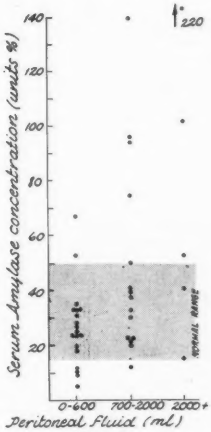


FIG. 2.



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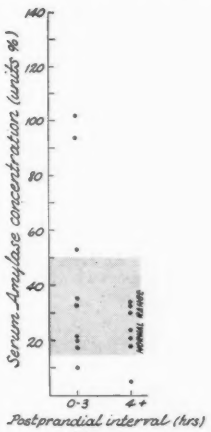

FIG. 4.

FIG. 1. Relation of serum amylase concentration to interval following perforation.

FIG. 2. Relation of serum amylase concentration to size of perforation.

FIG. 3. Relation of serum amylase concentration to amount of fluid in peritoneal cavity.

FIG. 4. Relation of serum amylase concentration to postprandial interval.

disease processes, but must be taken in proper perspective with the clinical findings. An upright roentgenogram of the abdomen, demonstrating free air under the diaphragm, was of considerable aid in several of our patients in whom high serum amylase concentrations were obtained.

The mechanism by which a rise in serum amylase occurs following an acute perforation of gastroduodenal ulcers has not been clearly demonstrated. Nemir demonstrated elevations of the serum lipase in dogs following the experimental production of appendiceal peritonitis and concluded that the rise was due to peripancreatic inflammation. Other authors have thought this to be the explanation of their findings in patients. In most reports, however, with specific comments, the pancreas has been described as grossly and histologically normal.

Pemberton, working with dogs in which duodenal perforations had been produced, demonstrated that amylase was absorbed from the peritoneal cavity in quantities sufficiently large to produce a rise in the serum concentration. He found that a rise was rarely observed unless the perforation occurred in the early postprandial period at a time when stimulation of the pancreas had resulted in a high concentration of the enzyme in the duodenal fluid. The fact that the highest elevations are seen in patients who have large perforations with large amounts of fluid in the peritoneal cavity would also support this hypothesis. However, under such circumstances secondary pancreatic inflammation would likely occur. Consequently, the main point in favor of Pemberton's theory of duodenal leakage and peritoneal absorption of the amylase is the negative evidence that definite pancreatic pathology has rarely been demonstrated.

SUMMARY

A preoperative serum amylase determination was performed upon 51 patients with acute perforation of gastroduodenal ulcers. Eight (15.7 per cent) had values above normal levels. An elevated amylase concentration occurred most often when the interval following perforation was greater than 12 hours, when the time lag following the ingestion of a meal was less than 3 hours, or when the perforation was large and the degree of soiling of the peritoneal cavity extensive.

Since an elevation in the serum amylase concentration may follow an acute gastroduodenal perforation, this finding can never be absolute in the differential diagnosis between acute pancreatitis and a perforated ulcer.

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TRIETHYLENE MELAMINE IN THE MANAGEMENT OF FAR ADVANCED OVARIAN CANCER

M. P. SYKES, M.D., R. W. RUNDLES, M.D., V. K. PIERCE, M.D., F.A.C.S., and D. A. KARNOFSKY, M.D., New York, New York

THE NITROGEN MUSTARDS,[1] which are principally used in the treatment of the lymphomas and chronic leukemias, have occasionally produced temporary therapeutic effects in some cases of far advanced inoperable carcinoma. The most striking results have been reported in lung cancer. Other types of carcinoma have not been explored as systematically or extensively, although there is ample evidence that the use of nitrogen mustard in gastric carcinoma, dysgerminomas, ovarian cancer, and breast cancer may result in temporary improvement (3).

When other types of polyfunctional alkylating agents became available, such as triethylene melamine (TEM) and related compounds, their effects in cancer were investigated. They produced occasional therapeutic effects in carcinoma, but there have been few systematic explorations of their value in specific forms of cancer.

In 1952 Rundles reported marked clinical improvement in 3 out of 4 cases of ovarian carcinoma treated with TEM. The useful degree of response obtained in these patients led to the treatment of a larger series at Memorial Center in order to determine the activity and role of TEM in ovarian carcinoma. Since Rundles' original cases were not reported in detail, they are included in this report.

From the Chemotherapy and Gynecology Services, Memorial Center, the Division of Clinical Chemotherapy, Sloan-Kettering Division, Cornell University Medical College, New York, N.Y. and the Department of Medicine, Duke University School of Medicine, Durham, N.C.

This work was supported by research grants from the American Cancer Society, the Damon Runyon Memorial Fund for Medical Research, the Lasker Foundation, and the Grant Foundation, and by Grant C-1889 and Grant C-1843 from the National Cancer Institute of the National Institutes of Health of the United States Public Health Service.

[1]The nitrogen mustard commercially used is methyl bis (B-chloroethyl) amine hydrochloride (HN2), mustargen®.

MATERIALS AND METHODS

A total of 26 patients (22 from Memorial Center and 4 from Duke University School of Medicine) with carcinoma of the ovary proved by histologic section, were treated with TEM. All patients had been treated by surgery, and usually by x-ray therapy, and showed recurrent and progressive disease prior to chemotherapy.

The histology of the ovarian carcinomas was as follows:

Case No. (Source)	*Histologic type*
1–13 (Memorial) 14 (Duke)	Adenocarcinoma
15–17 (Memorial)	Cystadenocarcinoma
18–20 (Memorial) 21–22 (Duke)	Papillary adenocarcinoma
23–24 (Memorial)	Anaplastic carcinoma
25 (Memorial) 26 (Duke)	Pseudomucinous cystadenocarcinoma

The data on the individual cases are summarized in Table I.

TEM was given by the intravenous and oral routes (2). The intravenous daily dosage was usually 3 to 4 doses of 0.04 milligram per kilogram (2 to 3 mgm.). The injection was usually given into the tubing of an intravenous infusion since extravasation causes a severe local reaction. At the recommended dosage, nausea and vomiting rarely occurred, although the patients occasionally complained temporarily of anorexia.

TEM for oral use was available in 5 milligram scored tablets. The usual dose was 2.5 to 5.0 milligrams per day, for 1 to 2 days. The TEM tablet was taken 1 hour before breakfast, with plain water. Oral TEM was usually tolerated satisfactorily although about 50 per cent of the patients complained

TABLE I.—SUMMARY OF CLINICAL COURSES OF PATIENTS WITH OVARIAN CANCER TREATED WITH TEM

	Before TEM			*Following TEM*				
Case No.	*Age*	*Duration disease, months*	*Last previous therapy*	*General condition*	*Response to TEM*	*Duration of response, months*	*Subsequent therapy, course*	*Follow-up after TEM, months*
				ADENOCARCINOMA				
1.....	49	24	Surgery	Fair	None	0	X-ray, downhill	Died—6
2.....	55	14	Surgery	Poor	None	0	Downhill	Died—3¼
3.....	44	23	Surgery	Fair	None	0	8-azaguanine, downhill	Died—3¾
4.....	39	9	Surgery	Good	None	0	Intra-arterial HN2 and x-ray	Died—20
5.....	41	36	Testosterone	Fair	None	0	Intra-abdominal Au^{198} HN2, X-ray	Died—6¾
6.....	49	12	Surgery	Poor	None	0	Downhill	Died—¼
7.....	73	4	Surgery	Poor	None	0	Downhill	Died—1
8.....	61	3	Surgery	Fair	None	0	Downhill	Died—2
9.....	52	63	Radium	Good	Good subj.	17+	Disease controlled by maintenance TEM	17+
10.....	46	3	Surgery, x-ray	Poor	Good subj. & obj.	2	HN2, downhill	Died—5
11.....	53	16	Surgery	Fair	Good subj. & obj.	3	Surgery for intestinal obstruction	Died—7
12.....	43	14	Surgery, x-ray	Poor	Good subj. & obj.	11	HN2 and x-ray, downhill	Died—16
13.....	52	12	X-ray	Fair	Good subj., fair obj.	2	Surgery, x-ray	Died—6
14.....	55	9	X-ray	Poor	Complete remission	46+	No evidence of disease	46+
				CYSTADENOCARCINOMA				
15.....	42	116	Surgery	Fair	None	0	X-ray	Died—4
16.....	48	10	Surgery	Fair	None	0	Downhill	Died—8
17.....	47	4	Surgery, x-ray	Poor	Fair subj.	1	2, 6-diamino-purine, downhill	Died—12
				PAPILLARY ADENOCARCINOMA				
18.....	28	15	X-ray, testosterone	Good	None	0	Downhill	Died—14
19.....	55	8	Surgery	Good	None	0	X-ray, downhill	Died—1
20.....	39	5	Surgery	Fair	Good subj.	3	Surgery for intestinal obstruction	Died—4½
21.....	14	5	HN2, x-ray	Poor	Good obj. & subj.	5	Downhill	Died—7
22.....	67	44	X-ray	Poor	Good subj.	2	Surgery	Died—8
				ANAPLASTIC CARCINOMA				
23.....	48	4	Surgery	Fair	Good subj.	2	X-ray, downhill	Died—8
24.....	59	12	X-ray	Fair	Good subj. & good obj.	4	X-ray, intestinal obstruction	Died—13
				PSEUDOMUCINOUS CYSTADENOCARCINOMA				
25.....	56	11	Surgery	Fair	Good subj. & fair obj.	2	Ascites, downhill	Died—8½
26.....	51	30	X-ray	Poor	Good subj.	7	HN2, X-ray, downhill	Died—12

of anorexia, mild nausea or dizziness, presumably due to the drug, at some time during the course of the treatment.

The average course of oral TEM therapy was 20 to 40 milligrams during the first month. Dosage was determined at 1 to 2 week intervals on the basis of the patient's hematologic and clinical response. If satisfactory improvement followed the initial course, the patient was then given maintenance doses of TEM under careful hematologic control.

It is desirable to induce some degree of leucopenia with TEM, as evidence of an adequate trial of therapy. Excessive dosage, however, will cause severe leucopenia, thrombocytopenia, and bleeding, and the maximum bone marrow depression usually does not appear until 2 to 3 weeks after the last dose. It is this effect which is the chief hazard in TEM therapy, and necessitates careful administration of the drug.

RESULTS

The results of TEM therapy in individual cases are summarized in Table II. Of the 26 cases, 12 patients failed to show any therapeutic response. Eleven of these patients received an adequate course of treatment, as evidenced by the production of

TABLE II.—SUMMARY OF HISTOLOGIC DIAGNOSES, DOSAGE AND RESPONSE IN PATIENTS WITH OVARIAN CANCER TREATED WITH TEM

		Failures		Response					
				Subjective improvement			Objective improvement		
Pathologic diagnosis	Total No. cases	Case No.	Total TEM first month, mgm.	Case No.	Duration in months	Total TEM first month, mgm.	Case No.	Duration in months	Total TEM first month, mgm.
Adenocarcinoma	14	1	10.5*	9	17+	‡	10	2	7.2*
		2	10.0*				11	3	10.8*
		3	21.6*				12	11	8.0*
		4	30.0				13	2	7.5*
		5	8.0*				14	46+	
		6	8.0*						
		7	10.0*						
		8	4.0*						
	Totals	8		1			5		
Cystadenocarcinoma	3	15	9.4*	17	1	10			
		16	20.0						
	Totals	2		1					
Papillary adenocarcinoma	5	18	6.0*	20	3	11.0	21	5	†
		19	9.6*	22	2	22.5			
	Totals	2		2			1		
Anaplastic carcinoma	2			23	2	7.5*	24	4	10.0*
	Totals			1			1		
Pseudomucinous cystadenocarcinoma	2			26	7	35.0	25	2	7.2*
	Totals			1			1		
	Totals 26	12		6			8		

* I.v. dosage.
† INH 37 mgm. followed by TEM 7.5 mgm. p.o. weekly.
‡ Thio-TEPA 65 mgm. i.v. followed by TEM 5.0 mgm. p.o. weekly.

leucopenia. This failure group included 8 of 14 cases of adenocarcinoma, 2 of 3 cases of cystadenocarcinoma, and 2 of 5 cases of papillary adenocarcinoma. The average survival time in this group was 5½ months after the onset of TEM (¼ to 20 months), with the median survival of 3¾ months. Following is an example of a patient who failed to respond to TEM (Fig. 1).

CASE 7. A 73 year old woman was found to have diffuse carcinomatosis at laparotomy. One month later, she complained of weakness, weight loss, and anorexia; there was a suprapubic mass filling the entire lower abdomen, and there was evidence of partial, intermittent intestinal obstruction. At this time a course of TEM was given intravenously without therapeutic benefit. Autopsy revealed extensive intra-abdominal and cardiac metastases, and no histologic changes were seen attributable to TEM.

Six patients showed some degree of subjective response alone, although there was no evidence of a decrease in the size of their tumors. The type of subjective improvement consisted of increased sense of well being, decreased weakness, improvement in appetite, and decrease in pain. All of these patients received adequate therapy as evidenced by a fall in the leucocyte count. This group consisted of single cases of adenocarcinoma, cystadenocarcinoma, anaplastic carcinoma, and pseudomucinous cystadenocarcinoma, and 2 cases of papillary adenocarcinoma. The average survival time for the group was 11 months after the onset of TEM (4½ to 22 months +) with a median survival of 10 months.

Eight patients showed objective evidence of regression of the disease, as well as subjective improvement. In this group were 5 adenocarcinomas, 1 papillary carcinoma, 1 anaplastic carcinoma, and 1 pseudomucinous cystadenocarcinoma. The average survival time from the onset of TEM therapy was 12½ months (5 to 46 months +) with a median survival of 8 months. The follow-

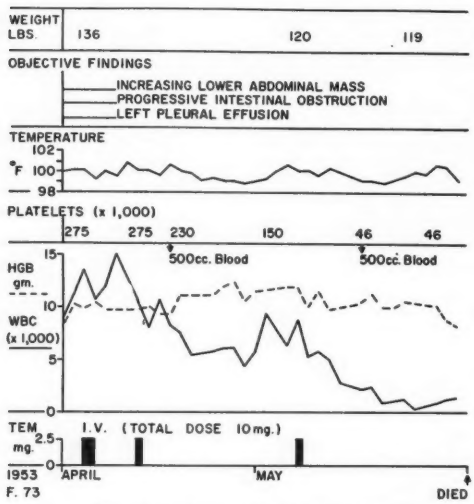

FIG. 1. Case 7. Patient with adenocarcinoma of the ovary who failed to respond to TEM.

ing brief histories demonstrate the type of response observed in patients who obtained objective improvement from TEM.

CASE 10. A 46 year old female had an exploratory laparotomy following a history of abdominal enlargement. Multiple carcinomatous implants were found. Two months later, another abdominal exploration revealed progression of the disease with ascites and a mass in the left lower quadrant. A course of x-ray therapy to anterior and posterior abdominal ports was commenced but had to be discontinued because of the development of partial intestinal obstruction with vomiting. The patient was maintained on intravenous fluids and given a course of intravenous TEM. This resulted in the relief of the obstruction, the abdominal mass was no longer palpable, and the patient showed marked symptomatic improvement and weight gain for a period of 2 months. The disease then recurred, failed to respond to intravenous HN2 and the patient died 5 months after the onset of TEM therapy.

A partial intestinal obstruction was relieved, and this patient showed conspicuous improvement for 2 months after a course of TEM.

CASE 11. A 53 year old female had an exploratory laparotomy following a history of crampy pain in the right lower quadrant. A carcinoma of the right ovary was removed, and a course of abdominal irradiation was given postoperatively. The disease recurred 1 year later, and laparotomy revealed carcinoma involving the surfaces of small intestine, sigmoid, omentum, and peritoneum. An omental mass was resected. Subsequently ascites, a fixed suprapubic mass, and a left pleural effusion developed; the latter containing cancer cells. The patient complained of intermittent attacks of diarrhea. A course of TEM intravenously was followed by a marked decrease in size of the suprapubic mass, decrease in pleural effusion and general symptomatic improvement. After a 3 month period, fever, diarrhea, and weakness occurred and despite further oral TEM the abdominal mass increased in size and pleural fluid reaccumulated. Intestinal obstruction developed 3 months later. A third exploratory laparotomy revealed ascites and multiple tumor nodules throughout the abdomen with adhesions of small and large bowel. A transverse colostomy was performed; the patient became febrile and expired 10 days postoperatively and 7 months after onset of TEM.

This patient had widespread abdominal and pleural disease which was partially improved for a 3 month period by TEM. The patient went steadily downhill for the remaining 4 months and further TEM was without benefit.

CASE 12 (Fig. 2). A 43 year old woman had a total hysterectomy and a bilateral salpingo-oophorectomy for an adenocarcinoma of the left ovary, followed by a course of x-ray therapy 14 months prior to admission to Memorial Hospital. At this time she complained of abdominal, pelvic, and low back pain and nausea and vomiting. A partial intestinal obstruction was present, and an irregular, firm, and tender mass filled the lower part of the abdomen, and another mass was felt constricting the lumen of the rectum. A course of intravenous TEM produced a marked decrease in the size of both the abdominal and rectal masses, relief of intestinal obstruction, and symptomatic improvement. She was maintained on oral TEM for a period of 11 months, during which time she gained a total of 15 pounds, and further reduction in the abdominal masses occurred. Signs of relapse appeared at the eleventh month when, despite continuing TEM, the abdominal masses increased in size, and fever, vomiting, and weight loss occurred. Twelve months after the onset of TEM therapy, she was given a course of intravenous HN2 (0.3 mgm./kgm.) and x-ray therapy to both anterior and posterior pelvic portals. This resulted in regression in the palpable pelvic tumors and complete relief of the chronic large bowel obstruction. Two months later, she developed minimal hemorrhagic tendencies and required readmission to the hospital, with complaints of lower abdominal pain, vomiting, weakness, and fever. These symptoms were improved with antibiotics and 2 blood transfusions. She, however, continued a progressive downhill course, developed a right hemiplegia due to

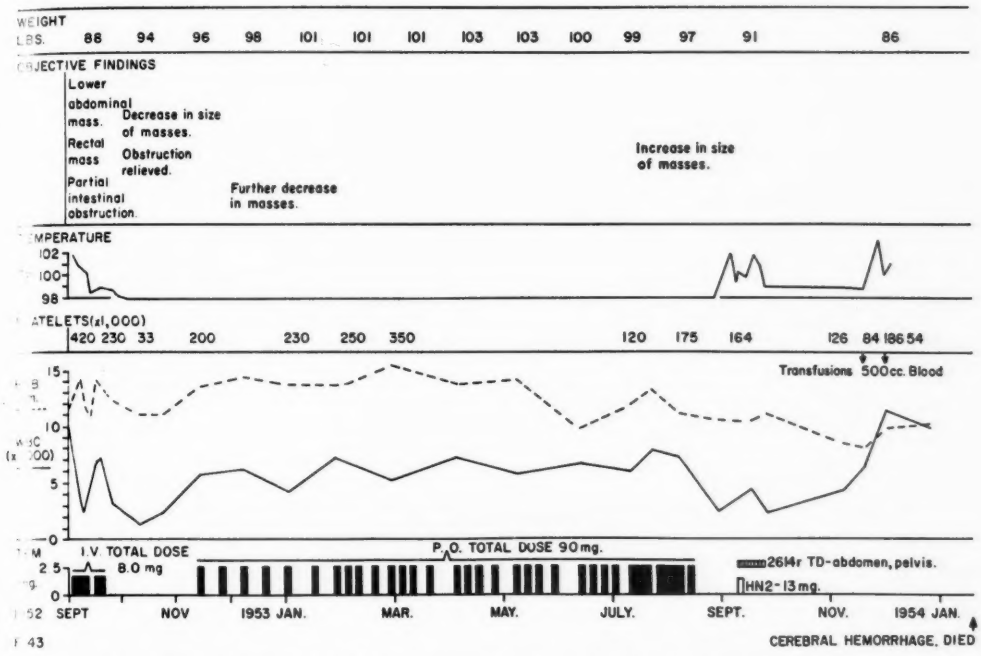

FIG. 2. Case 12. Patient with adenocarcinoma of the ovary, who obtained an 11 month period of objective improvement on TEM.

a cerebral hemorrhage, and expired 16 months after onset of TEM therapy. Postmortem examination demonstrated carcinomatosis with metastases to liver, spleen, pancreas, skin, bladder, right ureter, cervix, and peritoneum.

This patient, with recurrent ovarian cancer and a partial intestinal obstruction, following surgery and abdominal irradiation, obtained marked objective benefit from a course of TEM for a period of 11 months. She then became refractory to TEM and was briefly benefited by nitrogen mustard and x-ray for a period of 2 months. She died with widespread cancer, but a cerebral hemorrhage may have been related to her intensive TEM and nitrogen mustard therapy.

CASE 13. A 52 year old female complained of discomfort in the lower back and a change in bowel habits. Laparotomy, 6 months later, revealed inoperable bilateral adenocarcinoma of the ovaries, with metastases to the omentum. A course of pelvic and upper abdominal radiation was given. Symptoms recurred 6 months later, and physical findings were abdominal distention with a large mass in the right lower abdomen, a tumor infiltrating the pelvic floor, and a supraclavicular mass. TEM, intravenously, resulted in the disappearance of the supraclavicular mass and symptomatic improvement for 2 months. The disease then began to advance, and because of signs of obstruction a laparotomy was performed. Widespread abdominal carcinomatosis, with jejunal involvement, was present and the high obstruction could not be relieved by surgery. A course of x-ray therapy to the entire abdomen was without benefit, and the patient died 6 months after the onset of TEM therapy.

This patient, with widespread abdominal disease and an enlarged supraclavicular node, was considerably improved for 2 months on a course of TEM.

CASE 14. A 55 year old female experienced anorexia and lower abdominal pain. At laparotomy, a month later, hemorrhagic ascites was present, and a friable mass was found on the left ovary, with metastatic nodules on the omentum and intramurally in the

cecum. Bilateral salpingo-oophorectomy and omentumectomy were performed; the pathologic diagnosis was adenocarcinoma of the ovary. A course of x-ray therapy produced temporary improvement, but increasing abdominal distention, abdominal cramps, and constipation necessitated readmission to the hospital. On physical examination the patient showed evidence of weight loss, the abdomen was enlarged and tender, and the percussion note dull over the whole left lower quadrant. She was started on TEM by mouth. Two weeks later marked subjective improvement occurred, and there was a considerable reduction in abdominal girth. All evidence of disease then disappeared, and the patient remains asymptomatic 46 months after the initial administration of TEM.

This patient, who appeared to have progressive ovarian cancer following surgery and a course of x-ray therapy, showed complete regression of her abdominal symptoms after a course of TEM. She is well and apparently free of disease 46 months later. A spontaneous remission cannot be excluded in this unusual response.

CASE 21 (Fig. 3). A 14 year old female noticed increase in size of the abdomen, and at laparotomy an extensive tumor was found involving the pelvis, omentum, and abdominal wall. Pathologic diagnosis was papillary carcinoma of the ovary. A course of x-ray therapy was of transient benefit. The abdominal mass recurred, with dyspnea, anemia, and fever, and a hemorrhagic pleural effusion. The patient was treated with HN2, intravenously, followed by oral TEM. Objective improvement consisted of disappearance of abdominal mass and clearing of the pleural effusion for a 5 month period; and then despite continuing TEM therapy, the abdominal mass recurred and the disease progressed rapidly. Death occurred 7 months after the onset of nitrogen mustard therapy.

This patient relapsed following surgery and abdominal irradiation. A course of HN2 followed by TEM caused marked objective improvement for 5 months; but the disease then recurred despite continuing TEM therapy.

CASE 24. A 59 year old female initially complained of pain in the right flank and vaginal discharge, to be followed by abdominal enlargement. A laparotomy was performed and an inoperable anaplastic carcinoma of the right ovary was found. She received a course of x-ray therapy without benefit, and her abdomen continued to enlarge. When first seen at Memorial Hospital, large pelvic and left upper quadrant masses were palpated, and metastatic nodules were seen in the lungs by x-ray examination. A course of intravenous TEM was followed by objective evidence of regression of the pulmonary nodules, and symptomatic improvement, which continued for 4 months. Bilateral hydronephroses, due to enlarging abdominal masses, were then demonstrated by intravenous pyelography. A course of local x-ray therapy was given to the abdomen, while oral TEM was continued. The masses decreased in size, and symptomatic improvement occurred for 4 months. The patient then began to relapse, with recurrent episodes of urinary tract infection (controlled by antibiotics), anemia, and intermittent intestinal obstruction. Small doses of TEM were continued, but the disease progressed. Colostomy was performed because of intestinal obstruction, and peritoneal and visceral implants and liver metastases were found at operation. The patient died 1 month later and 13 months after the onset of TEM therapy.

This patient, after surgical exploration, did not respond satisfactorily to abdominal irradiation. A course of TEM produced tumor regression for 4 months; the disease recurred and responded to TEM and additional x-ray therapy, but then progressed inexorably.

CASE 25. A 56 year old female first noticed an increase in abdominal girth. A tumor of the left ovary was removed at laparotomy, and the pathologic diagnosis was pseudomucinous cystadenocarcinoma. A course of x-ray therapy was given but 2 months later ascites began to accumulate rapidly. Re-exploration showed widespread carcinomatosis, and a large mass of tumor was removed. Following the operation the patient presented a large mass in the right lower quadrant, cul-de-sac deposits, and marked abdominal distention. Intravenous TEM followed by oral TEM resulted in a marked reduction in rectal masses and a decrease in ascites for a 2 month period. The tumor then began to grow rapidly, and laparotomy was performed on several occasions and large masses of gelatinous tumor were scooped out to relieve distention. The patient continued to fail, and died 8½ months after onset of TEM therapy.

This patient, relapsing after surgical explorations and x-ray therapy, showed a 2 month period of objective improvement following a course of TEM.

Seven of the patients who showed objective improvement on TEM therapy, once relapse occurred on maintenance therapy, showed no further response to HN2 or TEM.

One case of adenocarcinoma of the uterine fundus was treated with oral TEM.

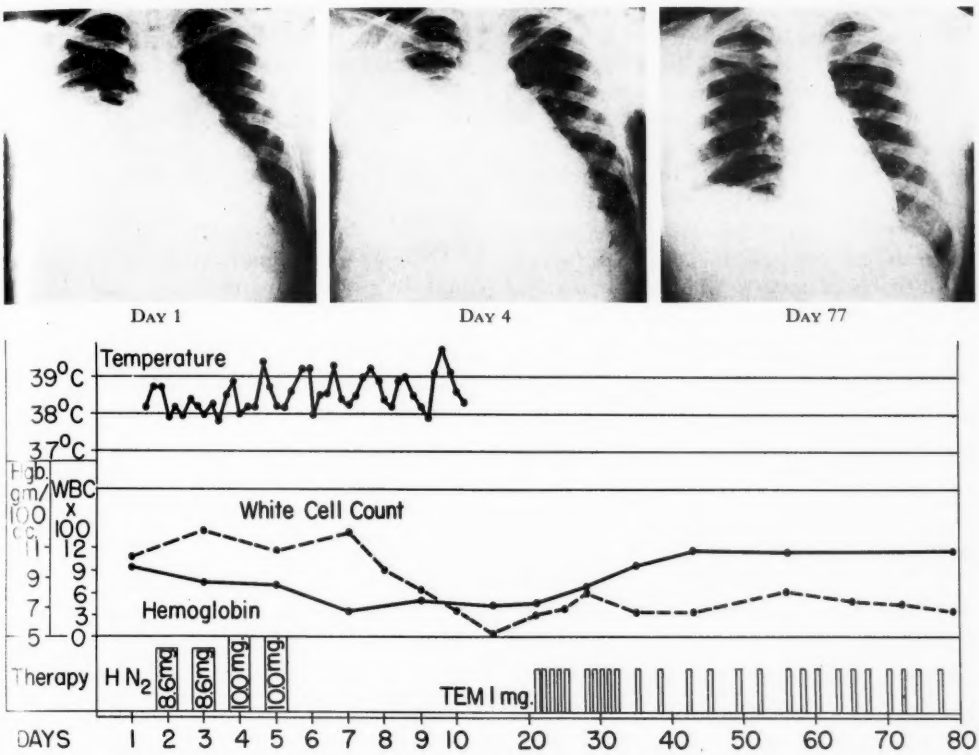

FIG. 3. Case 21. Patient with papillary carcinoma of the ovary who obtained a 5 month period of objective improvement on TEM.

The patient, a 54 year old female, first noticed irregular periods and spotting. A panhysterectomy was performed followed by x-ray therapy and testosterone. She did well for 6 months when she developed obstipation, melena, abdominal pain, anorexia, nausea, and weight loss. An exploratory laparotomy revealed generalized abdominal carcinomatosis and a loop colostomy was performed for a sigmoid obstruction. Because of the extensive disease she was given a course of oral TEM. This was followed by objective improvement for 4 months, as evidenced by disappearance of lymphadenopathy in the right groin and decrease in size of a rectal mass. The patient relapsed despite continuing TEM therapy, and she then received x-ray therapy to the pelvis. However, new masses surrounding the colostomy appeared and a palpable liver continued to enlarge. The patient died 12 months after the onset of TEM therapy.

This patient showed objective regression of carcinoma of the fundus following a course of TEM, and was considerably improved for 4 months, before the disease actively recurred.

DISCUSSION

Carcinoma of the ovary ranks in frequency behind carcinoma of the breast, cervix, stomach, large bowel, and fundus uteri in women, and because of its insidious and relatively asymptomatic onset, the 5 year cure rate is not high; Munnell and Taylor report an absolute 5 year survival of 30.8 per cent.

The consensus is that surgery is the treatment of choice, and that excision should be radical, consisting of hysterectomy, bilateral salpingo-oophorectomy, and if possible, complete removal of the carcinomatous process. The advisability of postoperative x-ray therapy is debatable.

All the patients in our series were explored and excision of the cancer was attempted when feasible. Of the 26 patients, 24 had had x-ray therapy following surgery. In 2 patients, 1 (Case 19) received a course of intravenous TEM 4 months after surgery directly followed by x-ray therapy without therapeutic benefit and Case 7 received intravenous TEM 3 months after surgery with no improvement.

In the 24 patients to whom x-ray therapy was given following surgery, either because the disease was inoperable or because of recurrent disease, improvement or control of the disease occurred in 14 cases for an average period of 12 months, before evidence of recurrent disease appeared.

Following TEM therapy 14 patients (54 per cent) showed subjective improvement, and of this group 8 (31 per cent) were also objectively benefited. The therapeutic responses ranged from less than 1 to 46 months, with an average of 3.5 months. Two of these patients (Cases 9 and 14) showed an unusually good response; the latter patient has now shown no evidence of recurrent disease for 4 years, and the possibility of a spontaneous remission must be considered.

Of the remaining 12 cases, the average response was 2 months. In the great majority of patients the range of the period of improvement was thus 1 to 3 months. This is the same general duration of response seen in lung cancer, Hodgkin's disease, and chronic myelocytic leukemia after single courses of HN2 or TEM.

Because of the duration and relative consistency of response obtained in patients with far-advanced ovarian cancer, an adequate trial of TEM is indicated in such patients. Objective improvement following TEM may also, in some cases, indicate the desirability of treating persistent masses causing symptoms with local irradiation. It is our impression that TEM offers a slight but definite advance in the palliative management of far advanced ovarian cancer. Our results do not imply that TEM is necessarily the polyfunctional alkylating agent of choice. It was the compound studied in this report, and comparable series of patients have not yet been treated with nitrogen mustard (HN2), thiotriethylene phosphoramide (thio-TEPA) or triethylene phosphoramide (TEPA).

SUMMARY AND CONCLUSIONS

Twenty-six patients with far advanced and inoperable recurrent ovarian cancer were treated with triethylene melamine (TEM). Fourteen obtained some degree of symptomatic improvement, and of this group 8 showed objective evidence of tumor regression. The usual duration of improvement ranged from 1 to 3 months. One patient showed an 11 month period of benefit and another has now shown no evidence of recurrent disease for a period of 4 years. The latter case may represent a spontaneous remission. On the basis of these observed responses, an adequate trial of TEM or a related compound is indicated in patients with a nonresectable or recurrent ovarian cancer. TEM may precede, follow, or be administered concurrently with x-ray therapy.

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NASOPHARYNGEAL CARCINOMA

II. *Treatment with Urethane (Ethyl Carbamate) and Triethylene Melamine*

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URETHANE

URETHANE and other carbamates have aroused considerable medical interest in the past because of the diversity of their physiologic and therapeutic effects which have been observed. They have been reported to arrest growth, to incite tumor formation, to relieve bronchial asthma, to increase the potassium content of bronchial secretion in the cat, to exert a toxic action upon the rat liver, and to cause inflammatory lesions in the lungs of mice. Urethane has also been used as an anesthetic in animal experiments for many years.

Compounds of the carbamate group have been observed to suppress cell division in plants, bacteria, protozoa, and in animal tissue in vitro. In experiments in the use of urethane upon animal tissues in vivo, Haddow and Sexton found that growth was suppressed in the Walker rat carcinoma 256. They found that there was a modification in the cellular structure of the tumor, and suggested that this was due to an attempted differentiation of the tumor cells. Paterson and associates extended this study to a trial of urethane upon advanced cases of malignant disease in man. They found that in many cases there was a marked fall in the leucocyte count and therefore determined to test the drug in the treatment of leukemia. Of 32 cases of chronic leukemia, the total white cell count fell dramatically in all but 2, and in favorable cases the spleen and lymph nodes decreased in size and the hemoglobin level rose. These effects were only temporary as recurrences took place. The same workers gave urethane to 24 other patients with advanced cancer, and in 7 of these there was marked improvement including 1 case of lymphoepithelioma secondary in lymph nodes. Following the work of Paterson and his associates, urethane was used in many parts of the world in cases of malignant disease, including prostatic cancer, multiple myelomatosis, the reticuloses, nasopharyngeal carcinoma, and the leukemias. As a result of these trials, it was generally accepted that although urethane exerted a palliative and not a curative action, further investigation of its place in the treatment of cancer was warranted in view of the advanced and hopeless nature of many cases which had responded.

Urethane was found to have various toxic effects of which anorexia, nausea, and vomiting were the most common. Leucopenia, agranulocytosis, hypoplastic anemia, thrombocytopenia, liver damage, and loss of weight in excess of that accounted for by low caloric intake were observed. One case of primary carcinoma of the liver developing in a patient treated with urethane for myelogenous leukemia was reported.

Many views have been expressed regarding the exact mode of action of urethane but the subject is too vast and controversial to consider here.

URETHANE IN THE TREATMENT OF NASOPHARYNGEAL CARCINOMA

The only report of a large group of patients with carcinoma of the nasopharynx

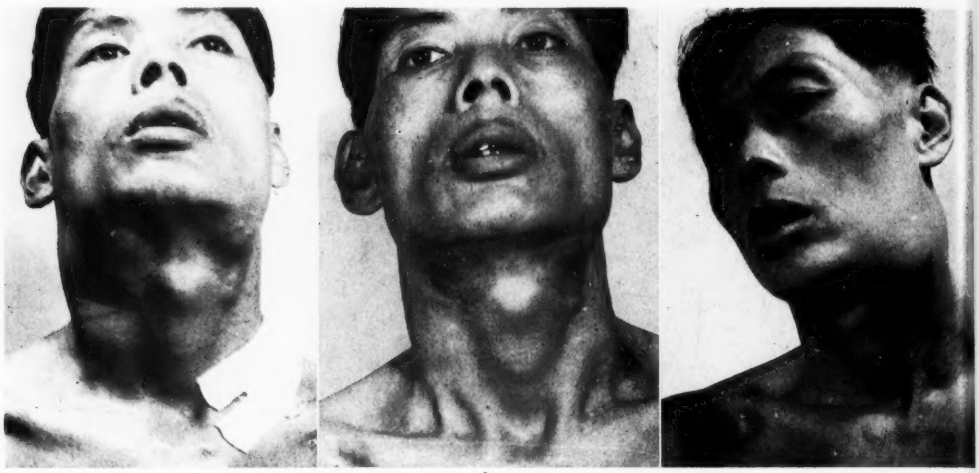
From the University of Malaya, Singapore.

TABLE I.—CLINICAL FEATURES, DOSAGE, AND RESULTS OF URETHANE THERAPY

Case No. Sex Age	Duration of symptoms mos.	Cervical adenopathy R.	Cervical adenopathy L.	Primary nasopharyngeal tumor detected	Cranial nerve lesion	X-ray evidence of cranial involvement	Distant metastases	Total dosage, gms.	No. of injections	Side effects	Lowest total WBC	Immediate results	Progress	Other treatment
1 F 18	7	x	x	x	x			72	6	Fever, giddiness, vomiting	4,000	Improved. Left cervical swelling disappeared; right persisted	Right cervical swelling increased. Left did not recur. Further progress unknown	
2 F 32	12	x	x	x	x	x		72 72 46.25	6 6 5	Vomiting	2,000	Improved. Lymph nodes decreased markedly in size. Died before completion	Died while under treatment, 14 mos. from onset	
3 F 15	14			x	x	x		39 39	6 6	Giddiness, nausea, vomiting, drowsiness	3,000	Improved. Nasopharyngeal tumor decreased in size	Died 3 mos. after urethane, 19 mos. from onset	Prefrontal leucotomy after urethane
4 M 51	4	x	x	x			x	78 52	6 4	Jaundice with acute liver enlargement	1,600	Improved. Cervical lymph nodes became rapidly smaller	Died 2 weeks after urethane, 6 mos. from onset	
5 M 33	18	x	x				x	63 63 63	6 6 6		2,200	Improved. Cervical swellings disappeared	Died 2 weeks after urethane, 20 mos. from onset	Radiotherapy before urethane
6 F 52	21	x	x					49.5 49.5	6 6	Copious vomoting	6,500	No result	Died 9 mos. after urethane, 31 mos. from onset	
7 F 51	16	x	x	x	x			9.75	1	Swinging temp. Vomiting	6,100	Discontinued	Died 7 months after urethane, 23 mos. from onset	
8 F 48	7	x	x		x			12	2	Anorexia++	7,000	Died before completion	Died while under treatment, 7 mos. from onset	
9 F 32	10	x	x	x	x			40	5	Vomiting	11,000	Refused treatment—no result	Unknown	
10 F 32	6	x	x	x	x			31.5	3	Vomiting, hematemesis, giddiness	4,300	Discontinued	Died 8 mos. after urethane, 14 mos. from onset	
11 M 35	6	x		x	x			33.75	3	Hematemesis	6,200	Discontinued	Died 6 mos. after urethane 1 year from onset	
12 F 47	4	x	x	x	x	x	x	47.1	6	Giddiness, ataxia, vomiting	4,000	Improved, became free of pain	Died 11 mos. after urethane, 15 mos. from onset	
13 M 60	12	x	x					29	2	Felt "drunk," anorexia, nausea	9,000	Refused treatment	Unknown	
14 M 38	1	x	x	x	x			82.5 27.5	6 2	Drowsiness, nausea	2,200	Improved. Cervical glands disappeared	Recurred in 2 wks.. Died 10 wks. after ureth., 6 mos. from onset	Radiotherapy during 2nd course of urethane
15 M	24						x		2	Drowsy then sleep. Nau-	4,700	Discontinued	Unknown	T.E.M.

15 M 45	24						x		2	Drowsy then sleep. Nausea, epigastric pain	4,700	Discontinued	Unknown	T.E.M.
16 M 37	24				x	x		64	4	Rigor, chest infection	7,000	Discontinued	Died 10 mos. after urethane, 34 months from onset	T.E.M.
17 M 37	6		x	x	x	x		70.5	6	Drowsy, rigor	2,800	Improved. Cervical glands disappeared	Recurred. Died 10 mos. after urethane, 17 mos. from onset	
18 M 41	7	x		x		x	x	66	6	Drowsy, rigor, shivering	3,100	Improved. Cervical glands decreased in size	Recurred after 4 mos., 15 mos. after urethane. Alive 22 months from onset	Radiotherapy
19 M 48	36	x		x	x	x		18	2	Rigor	8,600	Discontinued	Died 8 mos. after urethane 44 mos. from onset	T.E.M.
20 M 42	6		x					90	6	Drowsy, then hysterical. Giddiness, vomiting	4,000	Improved, cervical glands became much smaller	Recurred in 1 mo. Died 5 mos. after urethane, 11 mos. from onset	
21 M 52	36			x	x	x		70.5	6	None	8,000	No result	Unknown	
22 M 45	12			x				62.5	5	Dizziness	5,000	Improved—Primary smaller	Alive 14 mos. after urethane, 26 mos. from onset	Radiotherapy after 5th injection
23 M 52	2			x	x		x	32.25	3	Rapid deterioration	7,500	Discontinued	Died during treatment, 2 mos. from onset	
24 M 51	8			x				72	6	No reaction	5,000	No result	Unknown	Radiotherapy
25 F 33	6	x		x				9.5	1	Giddiness, nystagmus	6,500	Discontinued	Alive, 19 mos. from onset	Radiotherapy
26 M 44	30	x	x	x	x	x		30	3	Disorientated, anorexia, nausea	6,500	Refused treatment	Unknown	
27 M 36	6		x	x	x	x		33	6	None	5,000	No result	Died 8 mos. after urethane 18 mos. from onset	
28 M 53	6	x		x	x	x		40	4	Copious vomiting	5,000	Refused treatment	Alive, 8 mos. after urethane, 14 mos. from onset	
29 M 37	24	x	x	x	x	x		11	1	Rigor, vomiting	7,100	Discontinued	Alive, 4 mos. after urethane, 28 mos. from onset	
30 M 34	17	x		x			x		6	Anorexia, nausea	3,400	Improved slightly	Alive 2 mos. after urethane, 19 mos. from onset	

All details refer to time of commencement of urethane except progress which is calculated from time of completion of urethane.



a b c

FIG. 1. Case 14. a, Before urethane; b, at completion of first course; c, 3 weeks later, before second course.

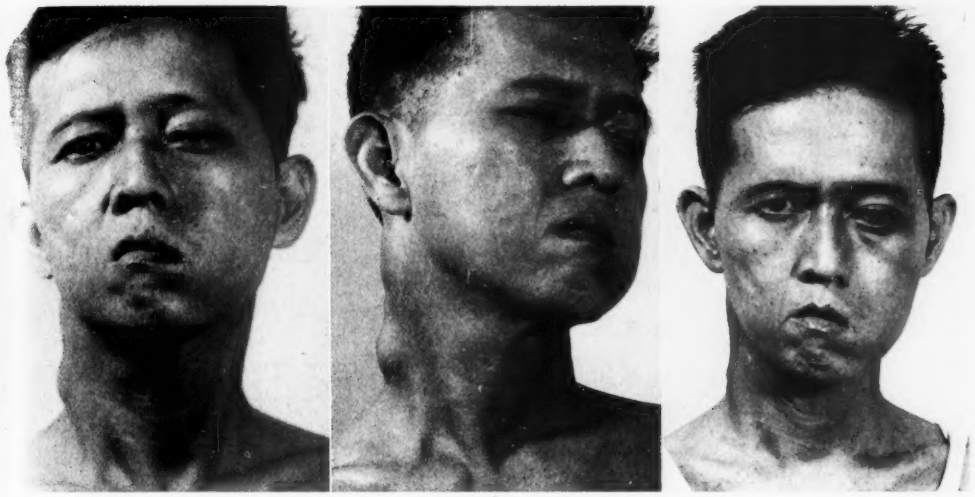
treated with urethane is that of Stock of Hong Kong. Of 23 patients, 5 died in hospital, 5 refused adequate treatment, 4 showed no improvement, 4 showed slight improvement, and 5 showed great improvement. Stock concluded that this form of therapy was worth following up as the disease did not normally regress spontaneously and suggested that it would be most useful if used in combination with radiotherapy.

Since 1951, 30 patients with nasopharyngeal carcinoma have been treated with urethane in the Civil General Hospital, Singapore. No fixed criterion was used in the selection of cases, but in the main the disease was advanced. Whenever possible, urethane was followed by a course of x-ray treatment.

Dosage and administration. Dosage was estimated according to body weight, 0.25 gram of urethane being given per kilogram of body weight, this being the dosage given to rats by Haddow and Sexton. In view of the severe side effects observed in the earlier cases it was later considered advisable to limit the dosage to a daily maximum of 12 grams. This dose was given daily for 6 days, but in several cases a day or more was allowed to elapse between doses because of systemic disturbances. Wherever possible a full course of 6 injections was given, and in a few cases 1 or 2 further courses were administered.

The method of administration was that advocated by Stock, the urethane being given intravenously. An intravenous drip of 5 per cent dextrose was set up and allowed to run for a few minutes. The urethane, which was dissolved in a quantity of sterile water varying from 20 to 30 cubic centimeters, was then injected into the tube with the dextrose still running slowly. The drip was immediately allowed to flow rapidly for 3 or 4 minutes, and then continued at a slower but still fairly rapid rate until 2 pints of dextrose had been given.

Routine investigations. A complete blood count, a photograph, an x-ray film of the skull, a record of the body weight, and biopsies of the nasopharyngeal or cervical lymph nodes were taken before treatment was begun. During treatment, a daily total count and differential white count were done. Hemoglobin level and weight were estimated at regular intervals. After treatment, further photographs and biopsies were taken wherever possible in all patients



a b c

FIG. 2. Case 18. a, b, Before urethane; c, after urethane.

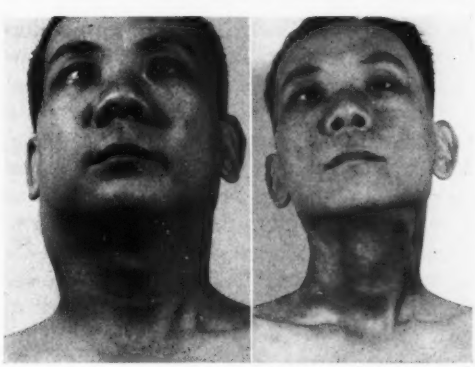
who had responded to therapy. The details of the clinical findings, dosage, and results of treatment are given in Table I.

RESULTS OF THERAPY

Sixteen patients completed one or more courses of urethane. This figure includes the patient in Case 22, who had only 5 injections but a total dosage of 62.5 grams and who started radiotherapy after the fifth dose.

Of these 16 patients, 12 showed improvement after urethane. In 9 of these the cervical lymph nodes decreased rapidly in size and in some cases disappeared entirely so that it was impossible to do a biopsy after urethane (Figs. 1, 2, and 3). In 1 case the adenopathy diminished only slightly. In 1 case in which there was no clinical involvement of the cervical lymph nodes, the primary tumor decreased in size. The remaining patient, also with no glandular enlargement, showed no change in the primary tumor but became symptom-free, whereas previously she had been in severe pain.

In the case of the remaining 4 patients who completed a full course of treatment there was no improvement. Of the other 14 who did not have a full course of urethane, 4 refused further therapy because of the systemic effects and 2 died while under therapy. Five patients had rigors and pyrexia accompanied in 2 cases by signs of an acute chest infection. One patient had immediate rapid nystagmus, lasting for 3 minutes and accompanied and succeeded by severe giddiness lasting for 5 days, and it was not considered justifiable to continue treatment. Three patients in whom vomiting was excessive, and in 2 cases bloodstained,



a b

FIG. 3. Case 17. a, Before urethane; b, at completion of treatment.

TABLE II.—RESPONSE TO URETHANE IN 30 PATIENTS

	Improved	*No result*	*Unable to tolerate drug*
Alive			
No.	3	0	3
Average duration of disease at present time, mos.	23	—	20
Average duration of life after urethane, mos.	10	—	10
Dead			
No.	8	2	7
Average duration of disease at death, mos.	12	22	19.5
Average duration of life after urethane, mos.	4	8.5	5.5
Unknown			
No.	1	2	4
Total No.	12	4	14

were not thought fit subjects for further urethane therapy.

Side effects. It is of interest to summarize the side effects of urethane which occurred in the 30 patients here treated. Anorexia and nausea were complained of by 21 patients; in 13 this progressed to vomiting, and in 2 cases to hematemesis. In 7 instances the leucocyte count fell below 3,000. There was no change in the differential white count. Five patients developed rigors, 2 with signs of an acute chest infection, and 1 patient had jaundice with an acutely enlarged liver.

This anesthetic action was demonstrated in 7 patients who became very drowsy while having the urethane administered and in some cases fell into a deep sleep. One patient said it made him feel "drunk," and another after an initial period of drowsiness became hyperexcitable and required sedation.

It is interesting to note that of the 12 patients who responded well to urethane, all but 1 had toxic symptoms ranging from anorexia to jaundice and a leucocyte count of less than 5,000. On the other hand, of the 4 who did not respond to treatment in spite of full dosage, only 1 exhibited any side effect of the drug, nor did the leucocyte count fall below 5,000 in any one of them.

Progress. In a previous study of 120 cases of nasopharyngeal carcinoma (5) it was found that the disease did not regress spontaneously and that the average expectation of life from the onset of symptoms was 13 months.

The improvement caused by urethane has never persisted for more than 4 months.

The progress of all 30 patients is given in Table II.

ADDITIONAL THERAPY

During urethane therapy, a soft fluid diet and a plentiful supply of glucose drinks were given.

When the total white cell count fell below 3,000, 10 cubic centimeters of a 10 per cent solution of pentose nucleotide were given daily for 7 to 10 days. In all cases the white cell count rose above 3,000 after this time.

One hundred grams of pyridoxine were given intramuscularly half an hour before urethane in the more recently treated patients and appeared to lessen the severity of anorexia, nausea, and vomiting.

Following the administration of urethane, 9 patients were given radiotherapy to which they all responded. Of 4 who had previously improved with urethane, 2 are still alive and 2 dead. Of the other 5 who did not respond to urethane (1 patient) or were unable to tolerate the drug (4 patients) 2 are alive, 1 is dead, and the progress of the other is unknown.

One patient who failed to respond to x-ray therapy later improved with urethane and is still alive. Triethylene melamine was given to 4 patients none of whom had completed a full course of urethane, and of whom 3 are dead and 1 untraced.

In 1 patient with advanced disease in whom the cervical lymph nodes had diminished in size after urethane, who had persistent intractable pain, a prefrontal leucotomy was performed (6). This patient died.

PATHOLOGY

Microscopically the tumors fell into the two main groups already described (4, 5): the large fleshy fungating growth and the small ulcerating lesion. There was no indi-

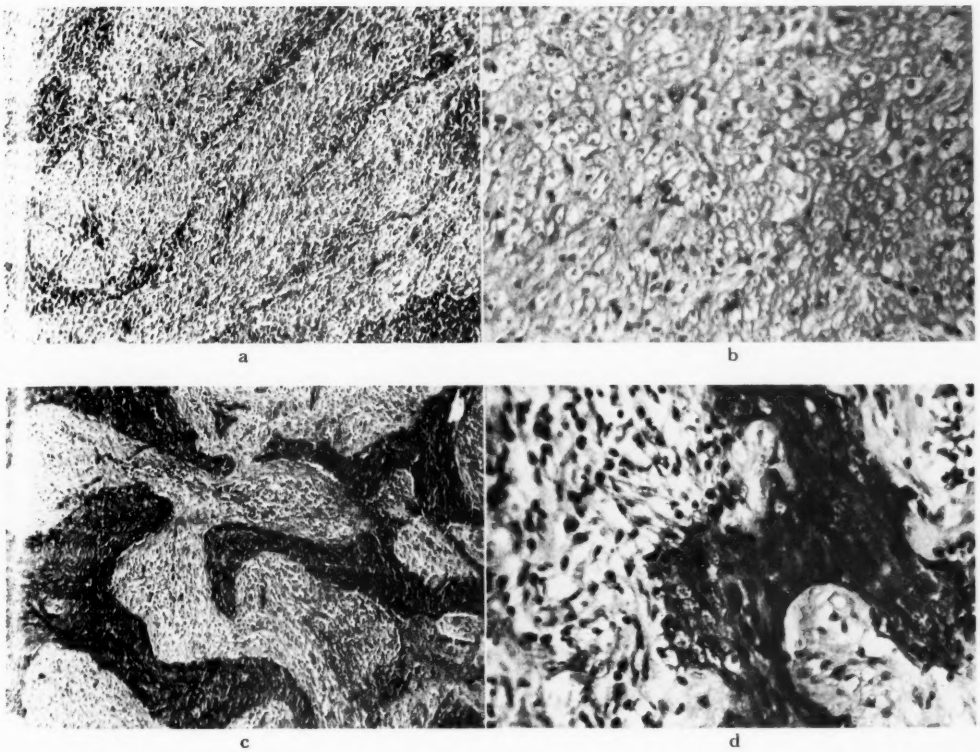


FIG. 4. Case 1. From cervical lymph nodes before urethane: a, low power; b, high power. From cervical lymph nodes after urethane: c, low power; d, high power.

cation that one type of growth reacted more favorably to urethane than did the other.

It is not within the scope of this article to enter into a discussion on the histogenesis of nasopharyngeal neoplasms. On microscopic examination of the tumors from the 30 patients, all appeared to be epithelial in origin. The degree of differentiation varied from tumors with definite squamous characters to extremely anaplastic carcinomas.

In 7 cases in which improvement occurred after urethane therapy it was possible to examine sections taken before and after treatment. In 5 of those there appeared to be an increased degree of differentiation of the tumor masses. The general architecture of the tumor presented a more defined appearance. The cytoplasm of the tumor cells became more easily distinguishable, the nuclei more pyknotic, and definite prickle cell formation could be identified where previously the cells had presented an ill-defined and anaplastic appearance. Mitotic figures were less common than before urethane. It is not suggested that this change was universal or that the entire tumor was completely transformed, but that these features could be recognized and gave an impression of increased differentiation. The stroma became more dense, vascular, and less cellular (Figs. 4 to 6).

In 2 cases the malignant cells appeared unchanged, but the tumor appeared more fibrous and vascular. There was no change in the frequency of mitoses.

POSTMORTEM FINDINGS

Postmortem examinations were carried out in 5 patients. Three of these had im-

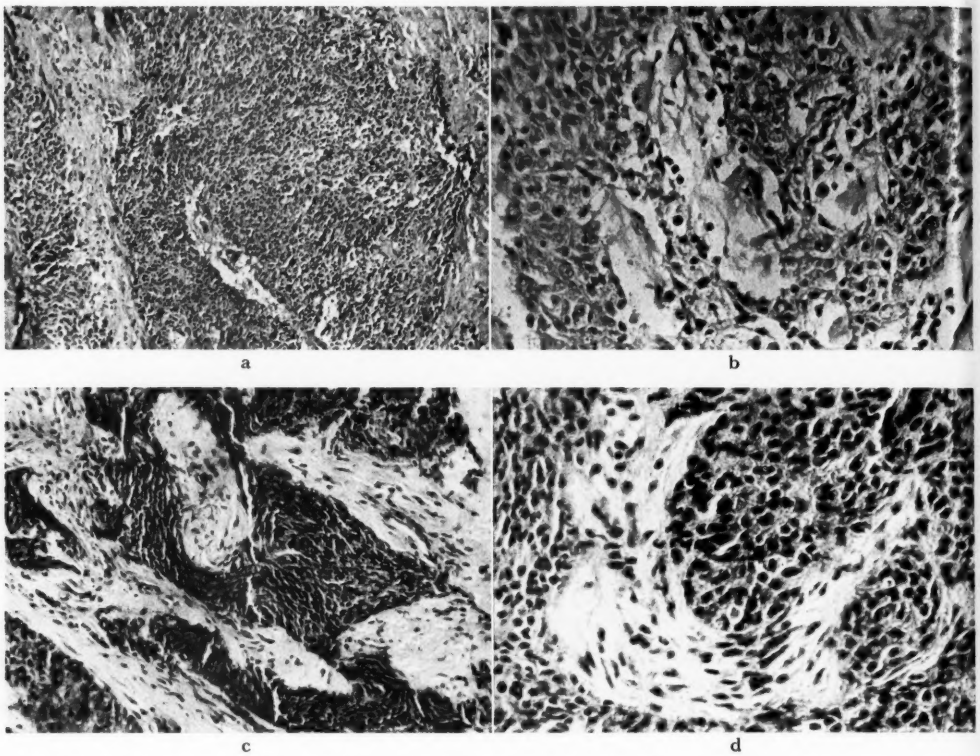


FIG. 5. Case 5. From cervical lymph nodes before urethane: a, low power; b, high power. From cervical lymph nodes after urethane: c, low power; d, high power.

proved with urethane and 1 had died during treatment. The other stopped treatment because of a chest infection. In Case 23, treatment was abandoned because of rapid deterioration in the patient's condition and severe cough with hemoptysis. At postmortem there were widespread pulmonary metastases. The liver appeared normal. The patient in Case 5 died 2 weeks after the completion of urethane therapy. The cervical lymph nodes had diminished in size after treatment, but autopsy revealed secondary deposits in the mediastinal lymph nodes, lungs, pericardium, ribs, and spine. Examination of the liver revealed no abnormality. The patient in Case 14 died 10 weeks after urethane therapy, having completed one course and started a second. Treatment was stopped as the veins were very thrombosed. He responded extremely well to urethane and later to radiotherapy. At postmortem, metastases were found in cervical, mediastinal, and paratracheal lymph nodes, lungs, and spleen. He had a terminal lobar pneumonia. The liver was normal on naked eye and microscopic examination. The patient in Case 16 died 10 months after urethane having been treated in the interval with triethylene melamine. Before death, he developed hyperpyrexia and lost consciousness. After death a secondary tumor was found at the cerebropontine angle, and there was mucopurulent exudate in the bronchi. The liver was normal.

The patient in Case 4, a Cantonese man of 50, was first seen with a 4 month history of swellings on both sides of his neck. He gave no other history. On examination he had bilateral large masses of cervical lymph

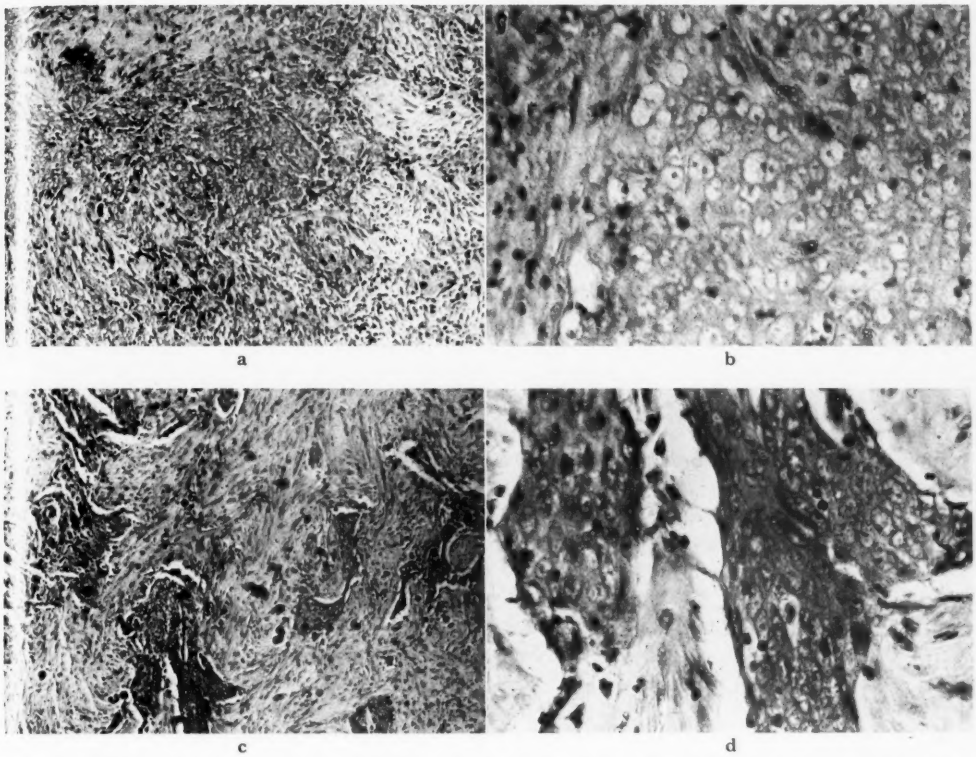


FIG. 6. Case 30. From cervical lymph nodes before urethane: a, low power; b, high power. From cervical lymph nodes after urethane: c, low power; d, high power.

nodes which were hard, nodular, and immobile. A gland was removed for histologic examination and reported as lymphoepithelioma. One month later he developed bilateral submental, submandibular, and axillary adenopathy and enlargement of the left supraclavicular lymph nodes. A tumor was felt on the posterior nasopharyngeal wall.

He was given a full course of urethane during which there was a visible diminution in size of the cervical, submental, submandibular, and supraclavicular lymph nodes. This course was followed within 3 days by a further 4 injections when thrombosis of the veins made further treatment impossible after which total white cell count fell to 1,600 and pentose nucleotide was used.

Eight days after the completion of therapy he became jaundiced, and this steadily deepened. In a further 5 days the liver was felt to be enlarged, he had ascites and urobilin was found in the urine. The following day he died.

At autopsy the liver was enlarged and congested with a nutmeg-like appearance. No metastases were found in the liver. There were bilateral pleural effusions and both lungs were edematous. The spleen was congested.

DISCUSSION

Several points emerge in analyzing the results of urethane treatment.

Twelve patients out of 30 improved with urethane, the maximum duration of improvement being 4 months. Eight of these patients were dead within 11 months of treatment. Of the 2 who have survived for any

length of time after urethane, both had subsequent radiotherapy so that the effect of urethane cannot be assessed. The combined form of treatment does not appear to give better results than does radiotherapy alone.

The average expectation of life in all cases of nasopharyngeal carcinoma has been found to be 13 months from the onset of the disease (5). The administration of urethane does not appear to prolong the patient's life. There was no significant difference between the duration of life after urethane in those who improved and those who failed to respond to or could not tolerate urethane. Nasopharyngeal carcinoma does not, as Stock has observed, regress spontaneously and yet in 12 out of 30 patients urethane has produced a marked improvement, causing either the primary tumor or the cervical metastases to diminish or disappear. Admittedly, this effect is not permanent but as a form of palliative treatment for these patients, urethane may have a place in therapeutics. When radiotherapy is readily available there does not appear to be much indication for urethane. If radiotherapy is not available or the disease is too advanced for such treatment, urethane may improve the patient's physical and mental outlook for a time.

This work was undertaken in the nature of an experiment, but the impression was gained that if the patient is forced to wait several weeks before commencing x-ray treatment, urethane may be of use in causing a regression in the growth of the primary nasopharyngeal tumor and the cervical metastases if this can be maintained until radiotherapy begins.

The toxic effects of urethane present a definite drawback to treatment. Nearly half the patients in this series were unable to tolerate the drug. The toxic symptoms in those who completed urethane therapy were much more marked in those who improved than in those who did not. Several of the patients in whom treatment was abandoned had already improved with urethane. The therapeutic and the toxic doses of the drug appear to approximate each other very closely.

The toxic effects were on the whole unpleasant but not dangerous. Anorexia, severe nausea, and vomiting were frequent findings but passed off quickly on completion of therapy. These effects are obviously due to systemic action of urethane and not to gastric irritation as suggested by Berman and Axelrod when the drug was given by mouth.

In only 1 case was there any suggestion that urethane had a fatal effect. This was in Case 4, already fully described. This patient developed jaundice, and an acutely enlarged liver and died within 2 weeks of completing urethane. At postmortem the liver was enlarged and resembled a nutmeg liver. Unfortunately, no histologic section from the liver is available, and, therefore, the extent or nature of the damage is not known. The postmortem signs were of severe congestive cardiac failure. Meacham and his associates have reported a case of liver damage in a patient treated with urethane for multiple myelomatosis. Here the lesions were similar to those of chronic passive hyperemia except that in their case there was edema and necrosis of the walls of the central hepatic veins and portal blood vessels. They found that these lesions were similar to those described in the liver of rats after urethane, and to those in man described by Ohler and his associates.

Obviously no conclusion can be drawn in the present case, but as liver damage is known to occur after urethane the appearance of jaundice and death after its administration are suggestive.

The occurrence of acute chest infections in 2 patients while under urethane treatment is interesting in view of the work of Orr who produced inflammatory lesions in the lungs of mice. Previously, pulmonary adenomas had been produced in mice with urethane, and Orr explained this as a secondary change in the inflammatory lesions. One of these 2 cases came to postmortem when the lungs were found to be normal. Three other patients had pulmonary metastases at autopsy, and although nasopharyngeal carcinoma does metastasize to the lung in the late stages

it is interesting to speculate whether urethane may produce an initial lesion in the lungs which predisposes to the occurrence of secondary cancer deposits.

The histologic study of these tumors is of interest in view of the work of Haddow and Sexton. They thought that after urethane there was an attempted differentiation of the tumor cells themselves. They noted changes in the vessels and stroma, but did not think the differentiation was secondary to these. In the sections studied here a similar attempted differentiation on the part of the malignant cells did appear to take place after urethane.

It is realized that any conclusions drawn here are not statistically significant.

SUMMARY

1. Thirty patients with nasopharyngeal carcinoma have been treated with urethane.

2. Of 16 who completed a full course of treatment 12 improved and 4 did not respond.

3. The improvement caused by urethane was found to be only temporary. The progress of all 30 patients is discussed.

4. Histologically the tumors appeared more differentiated after urethane than before.

5. Postmortem findings in 5 cases are recorded.

6. The possibility of using urethane as a form of palliative treatment is considered when: (a) radiotherapy is not available; (b) the disease is too advanced for radiotherapy; (c) there is an interval before the patient can commence radiotherapy.

Triethylene Melamine

Triethylene melamine (2, 4, 6 triethylamino-S-triazine), a nitrogen mustard-like substance was originally used in the textile industry to improve the finish of rayon fabrics. After the second world war its biologic effect on animal tissues was investigated, when it was found to have a therapeutic effect in leukemia in mice. Thereafter, a trial of triethylene melamine (TEM) in the treatment of leukemia and other malignant disease in man was instituted. It was observed to produce an improvement in chronic lymphatic and myelogenous leukemia, Hodgkin's disease, lymphosarcoma, and mycosis fungoides. Although the regression was of short duration in many cases, in some it was maintained for a considerable period. TEM was not found to be effective in carcinoma or anaplastic sarcoma.

Like urethane, triethylene melamine produced signs and symptoms of toxicity. These toxic effects are divided into two groups: (1) immediate which consist of anorexia, nausea, vomiting, and diarrhea and (2) delayed effects. The delayed actions of TEM which have been described include leucopenia, renal damage, eosinophilia, and hypoplasia of the bone marrow. Transient hematuria, raised blood urea nitrogen, and uremia have been reported. TEM appears to be equally toxic irrespective of its method of administration, nor is the degree of toxicity related to the dose given.

TEM IN THE TREATMENT OF NASOPHARYNGEAL CARCINOMA

Triethylene melamine was given to 7 patients with advanced cancer of the nasopharynx. Four had first been treated with urethane which they were unable to tolerate.

All 7 patients had large nasopharyngeal tumors, 6 had metastases in the cervical lymph nodes, and 5 had cranial nerve lesions associated with erosion of the base of the skull in 3 cases. One patient had a metastasis in the cervical spine and 1 had a secondary deposit in the sternum.

Dosage and administration. Five patients were given 2.5 milligrams of TEM daily for 4 days, and 1 had the same dose for 6 days. The first patient treated had only 1 milligram daily for 4 days. The drug was given in tablet form by mouth and was taken with a glass of water 1 hour before breakfast.

RESULTS

Improvement occurred in only 1 patient who had a total dosage of 15 milligrams of

TEM. This patient gave a 2 year history of bilateral cervical adenopathy; he had a large nasopharyngeal tumor and a large metastasis in the sternum. After TEM the sternal mass diminished slightly, but began to enlarge within a month. There was no change in the cervical lymph nodes or in the nasopharyngeal tumor. The total white cell count fell to 1,600 after 10 days and remained between 1,000 and 2,000 for 3 weeks in spite of pentose nucleotide injections. The polymorphonuclear leucocytes were affected more than the others, falling to 26 per cent at one point.

In the other 6 patients no improvement took place after TEM, nor were any of its toxic actions demonstrated.

The patient who improved was alive 3 months after TEM, but has not since been seen. Of the others, 4 died within 9 months of treatment, and 2 cannot be traced.

DISCUSSION

Only 1 patient out of 7 showed any response to TEM, and this improvement persisted for only a month. The administration of the drug was followed by a leucopenia and a marked fall in the number of granulocytes. TEM has previously been found ineffective in the treatment of carcinoma, and there does not appear to be an indication for it in the treatment of nasopharyngeal carcinoma.

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SURGICAL CLOSURE OF VENTRICULAR SEPTAL DEFECTS

Preliminary Report of New Technique

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IN THE PAST considerable confusion has existed concerning the clinical significance of isolated ventricular septal defects. For example, after studying 55 such cases which came to autopsy, Maude Abbott concluded that in this disorder symptoms were usually absent and cardiac function was seldom impaired. Moreover, Taussig considered the prognosis in small ventricular septal defects to be compatible with a long and active life. On the other hand, she called attention to the fact that these defects are of two general categories: the "simple" and the "high," each having a different prognosis. In the former type, generally known as maladie de Roger, the defect usually lies low in the septum and may be surrounded by myocardium (Fig. 1*a*). Although a loud murmur may accompany this type of defect, in general the disturbance in cardiac physiology is well tolerated. In the latter type of considerable size (Fig. 1*b*), however, the increase in the cardiac work load together with the alterations in the pulmonary vessels make the prognosis guarded. In a recent survey of the subject of septal defects, Selzer clarified the practical anatomic and physiologic features of the disease that determine and explain the variable clinical patterns which may be manifested. According to him, approximately 90 per cent of isolated ventricular defects and virtually all those associated with other malformations, are located in the membranous septum. In such instances the defect is a persistent interventricular foramen, characteristically present in fetal life but closing when the aortic septum fuses with the ventricular septum. Other defects in the septum represent only imperfections in development of the ventricular septum itself. Because of their position in myocardial tissue, the latter types of defects tend to constrict during systole reducing the volume of shunt, whereas defects in the membranous portion remain patent throughout the cardiac cycle. Furthermore, because of the spiral course of the upper portion of the septum, relatively large volumes of blood may be shunted from one chamber to another. If the aorta is displaced to the right, as in true Eisenmerger's complex, the volume of blood shunted may be enormous.

Although defects of the ventricular septum tend to be of more uniform size than atrial septal defects, their diameters may vary from 0.2 to 3 centimeters. Because of the variable degree of cardiac dysfunction in ventricular defects, depending upon their size, it is important to classify them into two groups on this basis. Thus, defects less than 1.5 centimeters in diameter usually cause few if any symptoms. Those between 1.5 and 3 centimeters in diameter, however, tend to cause significant cardiac disability. Griffin has confirmed these clinical observations experimentally by creating interventricular defects of varying diameters. Indefinite survival was possible with defects ranging from 8 to 10 millimeters in size and all tended to close spontaneously in a few weeks to several months, whereas defects of 12 millimeters were usually fatal. Bailey and associates have reported similar experiences. According to Taussig, congenital interventricular defects seldom, if ever, heal spontaneously; nevertheless reduction of size of the defect

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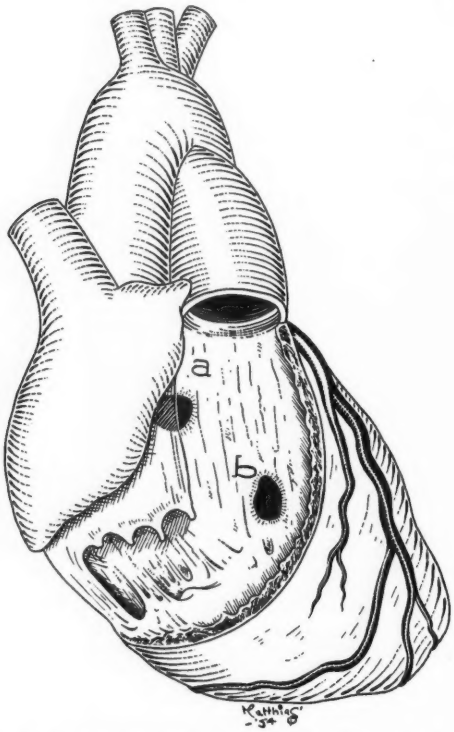

FIG. 1. Drawing showing ventricular septum with right ventricle removed showing positions where septal defects may be located. Defects located in the muscular portion of the septum (*a*) are well tolerated functionally, whereas high defects in the membranous portion of the septum (*b*) may be associated with serious cardiac disturbance.

by even partial closure may stimulate surrounding tissues to close the remainder of the defect spontaneously.

Relatively few successful methods of surgical closure of interventricular defects have been reported. Temporary circulatory arrest by general body hypothermia has been used successfully by Swan and Scott in several cases of ventricular defects, some in association with tetralogy of Fallot, but this procedure is somewhat hazardous and may be associated with air embolism or serious cardiac arrhythmias including ventricular fibrillation. Bailey and associates passed a pedicled pericardial tube through the defect in 3 patients in an attempt to plug the opening. In 1 patient who had tetralogy of Fallot, the tube had to be removed because it obstructed the small right ventricular outflow tract; but the other 2 patients with isolated ventricular defects survived, their defects being partially occluded. Kay reported a single case in which sutures were ingeniously passed through an interventricular defect under digital guidance, the ends of the sutures being brought out through the cardiotomy incision and tied. Whether or not the defect was completely closed was not stated, but 3 months later the patient's dyspnea was considerably improved. Recently, Lillehei and Warden and associates reported brilliant results in utilizing a donor to provide basal circulatory requirements during periods of circulatory arrest up to 24 minutes. Only 1 of the 4 patients whose defects were closed died. Obviously, however, this technique has a number of disadvantages including particularly the potential threat to the donor. Perfection of a practical and safe mechanical cardiac pump-oxygenator for temporary total substitution for the heart and lungs undoubtedly will solve many problems still confronting cardiac surgeons, but meanwhile other methods of correcting septal defects must be devised to salvage the more desperately ill patients.

Recently Björk and Crafoord modified techniques previously described in 1948 by Murray and later modified by Sondergäard for closure of atrial defects by a purse string suture-ligature of the septum. This procedure has great practical usefulness (4). Murray also utilized a similar method of passing a suture of a ¾ inch strip of autogenous fascia lata on a long straight needle "from front to back" in the ventricular septum crossing the ventricular defect. By tightening and securing the single suture by additional silk sutures at both points of exit from the heart he was able to reduce the size of the defect and also partially occlude it by the bulk of the suture. Two of the 3 patients in whom this procedure was employed survived with satisfactory results.

In the present preliminary report, a modification of previous techniques of septal

suturing will be described in which mattress sutures are passed through the upper third of the ventricular septum to close defects in the membranous portion, and experience with 2 patients thus treated will be related.

ANATOMIC CONSIDERATIONS

In order to close high ventricular septal defects effectively by means of mattress sutures passed in the plane of the septum, certain anatomic problems concerned with their insertion must be considered. In the first place, the sutures should not interfere with the outflow tracts of either the right or left ventricles. Inspection of the anterior surface of the beating heart reveals that the conus arteriosus of the right ventricle lies exactly anterior to the thickened interventricular septum and left ventricular outflow tract. Experimentally, a mattress suture, passed on a long curved needle in the septum, can be tightened without appreciable obstruction to cardiac outflow (Fig. 2). Some distortion of the right ventricle results as the septum is compressed, but this does not affect the diameter of the passageway or its function. In the beating heart poorly placed sutures may be recognized immediately by evidence of adverse effect on cardiac action and then replaced in a more suitable region for functional purposes. Another consideration of prime importance is the possibility that the sutures will interfere with the coronary arterial supply to the ventricles. The right coronary artery takes origin from the right aortic sinus and passes forward between the conus arteriosus and right auricle (Fig. 2). It then follows the right coronary sulcus in the atrioventricular groove to the diaphragmatic surface of the heart where the posterior descending branch originates. The right coronary artery supplies branches to the right atrium and to the root of the pulmonary artery and aorta. Usually there is one major preventricular branch which supplies the anterior wall of the right ventricle. The left coronary originates in the left aortic sinus and passes for a short distance forward where it divides into two principal branches: the anterior descending and the circumflex. The anterior descending is referred to as the "artery of sudden death" because of its vital function in providing arterial blood to the ventricular septum and muscular left ventricle. Principal coronary arteries may be accurately avoided by inserting mattress sutures at a point just to the right of the anterior descending branch and beginning about 3.0 centimeters from its origin, passing upward and posteriorly first through the muscular septum and then through the membranous or upper portion of the ventricular septum, and exiting in the area posterior to the right coronary artery near the root of the aorta, avoiding injury to the aorta itself. Sutures secured in this anatomic plane do not interfere significantly with arterial supply to the ventricles (Fig. 2).

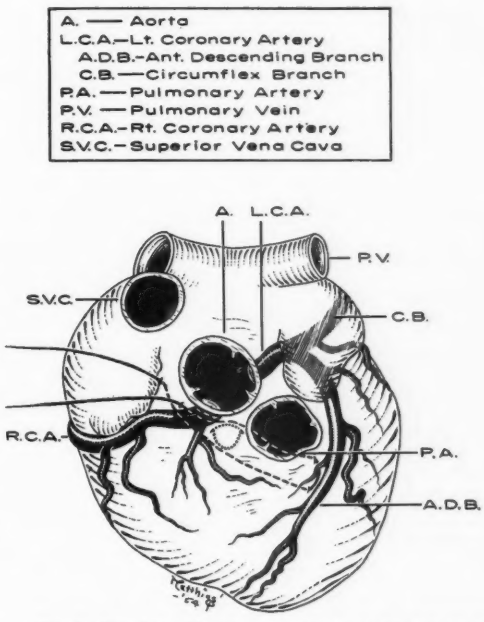

FIG. 2. Drawing of heart transected in a plane at level of semilunar valves showing anatomic relations of right and left ventricular outflow tracts and distribution of coronary arteries. Mattress sutures are passed through the septum and surrounding a high ventricular defect avoiding interference with ventricular outflow and coronary arteries.

Still another anatomic problem may be presented by the location of the conduction system of the ventricles. Although the atrial and ventricular portions of the myocardium are separate from each other, there is a small connecting band of specialized myocardium known as the atrioventricular bundle, which transmits the atrial impulse to the ventricles. The bundle begins in the atrioventricular node located in the septal wall of the atrium a short distance in front of the coronary orifice. The bundle passes into the ventricular septum posterior to the aortic valve and opposite the posterior leaflet, and then forward skirting the inferior margin of the membranous septum where it divides into right and left branches. The right and left bundle branches then continue downward in the muscular septum to their terminations. Mattress sutures placed into the ventricular septum in the ventricular outflow region adjacent to pulmonary and aortic valves tend to pass anterior and superior to the conduction bundles. Furthermore, according to Murray, passage of sutures through the septum, either experimentally or in patients, causes no ill effects from injury to the bundle of His; and theoretic objections to the procedure based on these grounds are of no practical importance.

TECHNIQUE

After administration of standard preanesthetic medication, endotracheal general anesthesia is induced with cyclopropane and ether. General body hypothermia may be useful in small infants, particularly in the most critical cases. With the patient in the supine position a transverse anterior submammary incision is made, usually through the fourth intercostal spaces bilaterally transecting the sternum (Fig. 3a). If there is a question of the presence of a patent ductus arteriosus or aorticopulmonary septal window, preliminary exploration can be accomplished through the left anterior third interspace. If a ventricular septal defect is discovered, this incision can be extended to the right across the sternum and into the corresponding contralateral interspace. The pericardium is widely incised transversely to expose the base of the heart.

The position of the ventricular defect may be determined by inspection and palpation of the surface of the right ventricle, where the jet-like stream is evident. In most instances, the anomaly is located behind the medial cusp of the tricuspid valve, the attachments of which may prevent easy intracardiac palpation of the septal defect particularly in small patients.

Closure of the defect is accomplished with a mattress suture of No. 0 or No. 1 braided silk on a large half-circle round needle. The first suture is started on the anterior surface of the ventricle about one-third of the distance from the root of the pulmonary artery to the apex of the right ventricle and just to the right of the anterior descending coronary artery. The suture is passed upward in the septum toward the root of the aorta and brought out posterior to the right coronary artery and through the adjacent right atrial tissue (Fig. 3b). In order to expose this sulcus behind the aorta, the right auricular appendage must be retracted laterally; and the point of the needle is palpated with the left index finger. As the needle appears posteriorly, it is grasped by the assistant and pulled through in the line of curvature of the needle. As the suture is being inserted, it is possible to feel the resistance offered by the septal tissue and determine with some accuracy when the needle traverses the septal defect. After one limb of the mattress suture has been placed, the anterior end of the suture is threaded on the needle and passed through the septum at a slightly lower level, exiting above posterior to the first limb of the suture (Fig. 3c). A free graft of striated muscle is placed inside the suture at the point of exit at the base of the atrium to prevent the suture from cutting through the atrial myocardium. The suture is then tied down slowly, the heart being observed closely for evidence that the position of suture will cause interference with cardiac action (Fig. 3d). If a thrill remains in the pulmonary artery

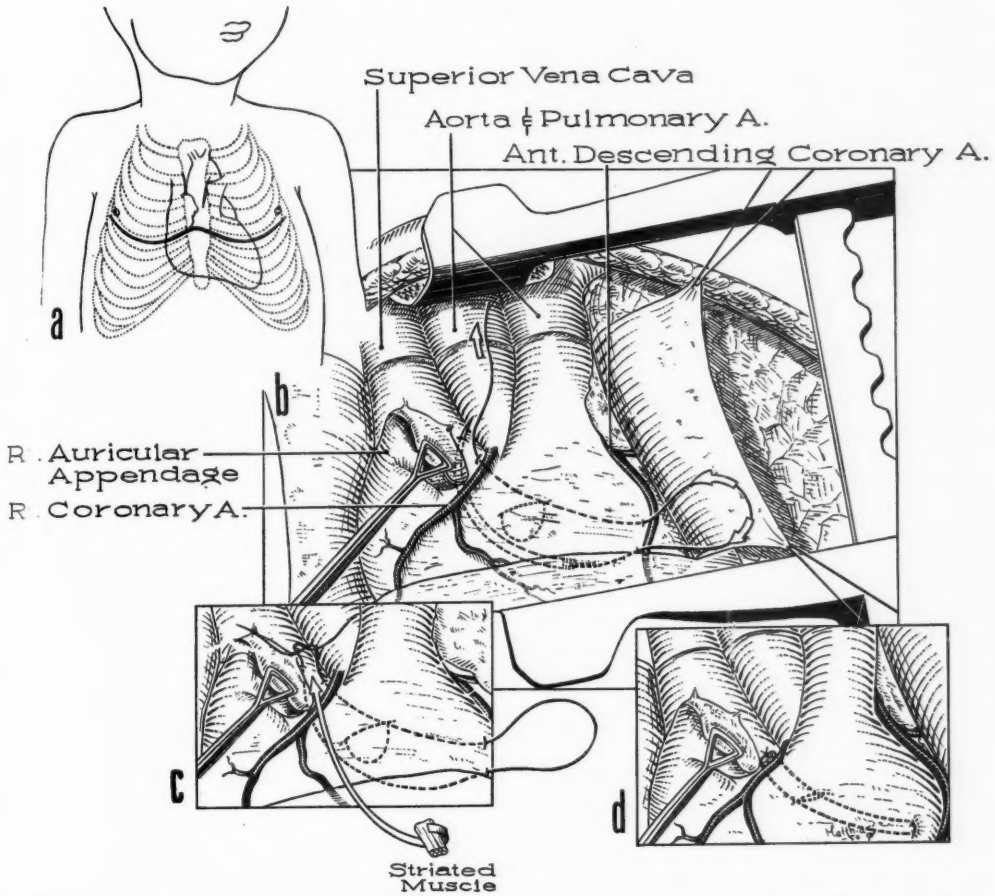

FIG. 3. Drawing showing technique of closure of interventricular septal defects. a, The incision for thoracotomy is shown entering the fourth interspace bilaterally and transecting the sternum. b, A mattress suture of No. 1 braided silk is placed through the septum. c and d, It is tied over a graft of striated muscle to obliterate the defect.

and conus after the suture has been tied, additional sutures should be placed farther down on the septum. Continuity of small transverse arteries originating from the anterior descending branch may be preserved by carefully slipping the suture behind them so that when it is tied down, the artery lies outside the mattress suture (Fig. 2). As many as 4 or 5 sutures may be inserted in the septum until the thrill has been eliminated or greatly reduced and until the pulmonary artery and right ventricle have strikingly decreased in size.

The pericardium is closed loosely, and the incision is approximated with pericostal and sternal sutures of chromic catgut. Catheters are inserted into both pleural spaces for underwater drainage.

REPORT OF CASES

CASE 1. A. L., 18 month old Latin American boy, was admitted to the Texas Children's Hospital on November 17, 1954. At 3 weeks of age, forceful, rapid heart beat was noted; and a diagnosis of congenital heart disease was made. He had had frequent respiratory infections, but never any evidence of cyanosis Weight gain and development were retarded.

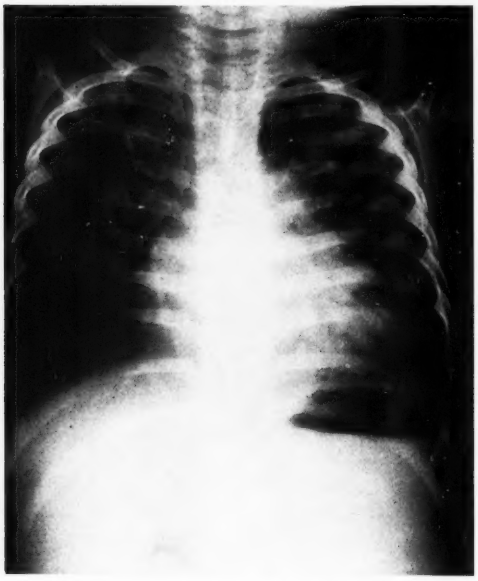

FIG. 4. Roentgenogram of chest in Case 1 showing right ventricular enlargement, dilatation of the main pulmonary artery, and increased pulmonary vascularity.

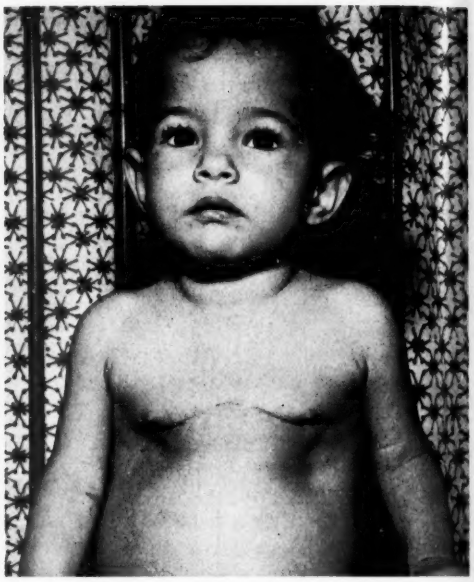

FIG. 5. Photograph of patient in Case 1 made 3 weeks after operation, showing good general physical condition and well healed incision.

Physical examination revealed an irritable, underdeveloped, pale, poorly nourished infant who weighed 15 pounds 10 ounces and appeared chronically ill. Mottling of the skin appeared on coughing. Blood pressure was 88 millimeters of mercury systolic and 60 millimeters of mercury diastolic; peripheral pulses were normal. There was a pigeon breast deformity of the sternum; the ribs were deformed over the precordium, which heaved strikingly with each heartbeat. A diffuse thrill, palpable during systole, accompanied a harsh systolic murmur, which was maximal in the third interspace to the left of the sternum. The pulmonic second sound was accentuated. Lungs were clear, and a firm edge of the liver was palpable 2 centimeters below the costal margin.

The hemoglobin was 12.9 grams per 100 cubic centimeter, hematocrit 42 per cent, and leucocyte count normal. Roentgenograms of the chest demonstrated cardiac enlargement involving predominantly the right ventricle, undivided pulmonary artery and left auricle (Fig. 4). There was fluoroscopic evidence of increased vascularity of the lungs. Electrocardiograms showed right ventricular hypertrophy and a first degree heart block.

On the day after admission, cardiac catheterization[1] performed through the right saphenous vein revealed the following:

[1]Performed by Dr. Dan G. McNamara.

	Blood oxygen content, vols., per cent	*Pressure, mm. Hg*
Inferior vena cava	7.1	0
Right auricle (mid.)	7.7	0
Right ventricle (apex)	11.5	68/0
(out)	10.9	62/0
Main pulmonary artery	11.5	60/12
Right pulmonary artery	11.9	54/12

Digitalization was slowly accomplished during the ensuing few days. Five days after admission, under ether anesthesia and by means of ice bags, body temperature was reduced to 90 degrees F. A transverse bilateral submammary incision was made through fourth intercostal space transecting the sternum. The pericardium was opened transversely, and about 30 cubic centimeters of clear fluid was evacuated. The right ventricle was dilated and hypertrophied, and there was a prominence in its outflow tract where a definite strong jet of blood could be felt originating in a high ventricular septal defect. An attempt to explore the right auricle digitally was abandoned because of cardiac irritability and impending cardiac arrest. Therefore, 2 mattress sutures were inserted and tied. The jet-like stream of blood and thrill disappeared in the right ventricular outflow tract, and there was a dramatic reduction in size of the entire ventricle and right auricle. There was a faint thrill persisting in the pulmonary artery. The sutures caused mild deformity in the outflow zone but did not interfere with blood flow. Cardiac action remained satis-

factory, and the pericardium was closed loosely. At the completion of the operation, the patient's condition was good. Rectal temperature was 88 degrees F. During the ensuing hour, body temperature was raised gradually to normal.

Except for a moderate febrile response on the day following operation, postoperative recovery was satisfactory. Digitalization was continued, and signs of pulmonary congestion subsided gradually after the first week. The incision healed primarily. On discharge from the hospital, on the twenty-fifth postoperative day, the patient weighed 16 pounds 8 ounces, was active and definitely improved (Fig. 5). A faint systolic murmur could be heard over the left third interspace, and roentgenograms of the chest revealed reduction in cardiac size and pulmonary vascularity.

CASE 2. C. J., a 9 year old white girl, was admitted to the Texas Children's Hospital on December 28, 1954, because of exertional dyspnea. At the age of 6 weeks, following a sudden syncopal attack lasting several hours, a loud cardiac murmur was first noted. Weight gain was poor during the first year of life, but since that time development had been good. The patient had had no further syncopal spells and had never been cyanotic. Dyspnea appeared after moderate exertion, however; and precordial and low dorsal pain had been experienced on occasions.

Physical examination revealed a fairly well nourished and developed child in no discomfort. Blood pressure was 100 millimeters of mercury systolic and 70 millimeters of mercury diastolic. Sternal prominence was evident. Precordial pulsation was accentuated, and harsh precordial thrill was palpable to the left of the sternum. A grade V systolic murmur was audible along the left border of the sternum, most striking in the second and third intercostal spaces. Pulmonic second sound was accentuated. The lungs were clear, and the liver was not palpable.

Results of routine laboratory studies were within normal limits. Cardiac enlargement involving both ventricles, and dilatation of the undivided pulmonary artery were visualized in the roentgenogram of the chest (Fig. 6). Fluoroscopy revealed increased pulmonary vascularity with vigorous pulsation. Angiocardiogram showed a dilated main pulmonary artery and delayed elimination of the contrast material from the heart and lungs, suggesting reopacification by a large left to right shunt. Electrocardiograms indicated left ventricular hypertrophy.

Cardiac catheterization, accomplished previously,[2] revealed the following:

	Blood oxygen content, vols. per cent	*Pressure, mm. Hg*
Superior vena cava	9.7	—
Right auricle	9.7	—
Right ventricle	13.9	42/0
Main pulmonary artery	13.7	35/10
Right pulmonary artery	13.5	38/12

[2]Performed by Dr. Ray H. Skaggs at the Methodist Hospital.

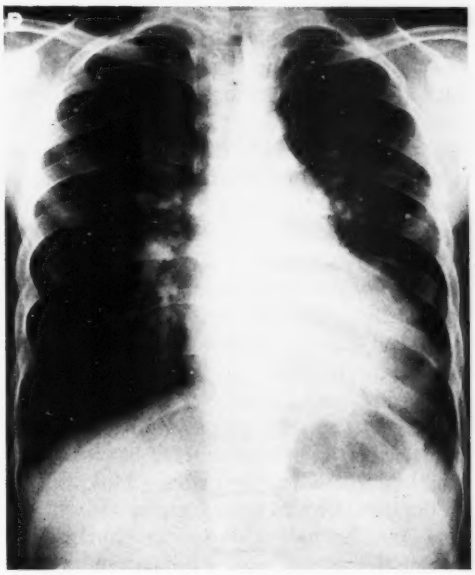

FIG. 6. Roentgenogram of chest in Case 2 showing enlargement of both ventricles, dilatation of the main pulmonary artery, and increased pulmonary vascularity.

Thoracotomy was performed on December 31, 1954, under ether anesthesia. Because of the possible existence of a large patent ductus arteriosus, a preliminary left submammary third intercostal space incision was made for exploration. The ductus arteriosus, which was ligamentous and completely obliterated, was severed. The pericardium was entered, and the source of the thrill was located in the conus arteriosus of the right ventricular outflow tract. In order that better exposure might be obtained, the sternum was transected, and the incision was extended into the third interspace on the right. The pericardium was widely opened. Four mattress sutures of No. 1 braided silk were inserted into the septum and tied down securely. The thrill in the conus and pulmonary artery was almost eliminated by the sutures, and the diameter of the main pulmonary artery was reduced from 4 to 2 centimeters. The child tolerated the procedure well without evidence of circulatory failure or serious cardiac arrhythmia. Blood samples were taken from the right atrium and main pulmonary artery, and blood oxygen content was 13.1 and 13.8 volumes per cent, respectively.

The postoperative hospital course was relatively smooth, and the patient was discharged on the fifteenth postoperative day. At discharge, a persistent systolic murmur could be heard along the left border of sternum, but character of the murmur, reduced pulmonic second sound, and clinical improvement indicated that defect had been almost closed.

SUMMARY

Isolated ventricular defects are in general associated with mild disability and disturbance in cardiac function depending upon their size and location. Defects located in the muscular portion of the septum cause relatively slight disturbances in cardiac function, whereas those located in the membranous septum may lead to obvious disability. Defects greater than 1.5 centimeters in diameter frequently increase cardiac burden significantly, leading to cardiac enlargement and ultimately to decompensation. In this group of patients, surgical correction assumes a necessary importance. A method is described in which mattress sutures may be passed through the septum to close high ventricular defects. Accurate placement of the sutures avoids interference with blood flow into the pulmonary artery and aorta, disturbance in function of the cardiac valves, and obstruction to coronary arterial supply to the myocardium. Two patients have survived operation by this technique and show early evidence of improvement.

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EXPERIENCES WITH 1,356 CASES OF CHOLECYSTITIS AND CHOLELITHIASIS

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CHOLECYSTECTOMY has become the second most frequently performed abdominal operation. It is exceeded in frequency only by laparotomy for removal of the appendix. The realization of the significance of gallstones, the increasing use of the Graham-Cole test, and the availability of good operating room facilities have all contributed to the large number of cholecystectomies being performed today.

Careful preoperative evaluation of the patient, modern anesthesia, improvements in operative technique, and better postoperative care have contributed to the low mortality and morbidity rates associated with this operative procedure at the present time. This is particularly true when the cholecystectomy is done by a well trained surgeon under good operating conditions.

Unfortunately, there is another and less favorable side to the problem of cholecystectomy. Gallbladders are still being removed for "noncalculous chronic cholecystitis," a condition in which cholecystectomy is of questionable value. Secondary operations on the biliary tract are performed all too frequently for stones remaining in remnants of the ballbladder, the cystic duct, or the common bile duct. The mortality and the morbidity associated with these secondary procedures must be added to that of the original operation. The number of patients who have had an injury to the common bile duct during the course of a cholecystectomy forms an unsightly blot on the record of modern surgery. Over 500 of these unfortunate individuals have been sent to this clinic because of this complication, one of the most serious that can occur during the lifetime of any surgeon. Many of these patients ultimately will die as a direct result of cholecystectomy. The fact that the original operation was often described as "very easy cholecystectomy," and the fact that it has occurred at the hands of men who are recognized as experienced surgeons are indications of the danger in the very frequency with which this operative procedure is being performed today.

For these reasons and many others it is of value for any surgeon or group of surgeons periodically to review his or their experiences with surgery of the biliary tract. It is important to know the actual operative mortality, the incidence of complications, and the number of, and reasons for, unsatisfactory results following cholecystectomy. The clinical records of 1,356 patients operated upon for disease of the biliary tract in the 4 year period from 1950 to 1953, inclusive, have been carefully reviewed. These may be compared in many details with an earlier group of 1,104 patients reported from this clinic (1) in 1947.

CLINICAL DATA

The average age of these 1,356 patients was 51.6 years. The youngest patient was a male 14 years of age. The oldest was 90 years of age. There were 327 patients over the age of 60 in this group (Table I). There were 873 females and 483 males, a ratio of approximately 2 to 1. Five hundred thirty patients, or 39 per cent, were either overweight or had been overweight. Twenty-one per cent of the entire group gave a history of a recent weight loss, whereas 50 per cent of those patients with a common duct stone had a history of recent weight loss.

From the Department of Surgery, The Lahey Clinic, Boston.

TABLE I.—AGE DISTRIBUTION: COMPARISON WITH PREVIOUSLY REPORTED STUDY

Age, years	*1942–1945 1,104 Patients*	*1950–1953 1,356 Patients*
10–20	6	3
21–30	70	71
31–40	206	162
41–50	312	323
51–60	313	470
61–70	196	269
71–80		52
81–90	1	6

Pain was the commonest symptom and was found in 1,187 patients, or 87.5 per cent (Table II). Only 1 of the 169 patients without pain proved to have a completely normal gallbladder. She had been operated on because of a roentgenologic diagnosis of calculi. Ten other patients were found to have chronic cholecystitis without stone. Seven patients with subacute or acute cholecystitis and 1 patient with a gangrenous gallbladder and stones had not complained of pain. Two patients without pain were found to have carcinoma of the common or hepatic ducts. The remaining 148 patients who did not give a history of pain were found to have chronic cholecystitis with biliary calculi.

Dyspepsia (belching and flatulence) was present in 861, or 63.5 per cent, and was the sole symptom in 67, or 4.9 per cent. Sixty-two of these patients whose only symptoms were belching and flatulence had chronic cholecystitis with stones, 4 had acute cholecystitis with stones, and only 1 had chronic cholecystitis without cholelithiasis.

Nausea and vomiting occurred in 661 patients, or 48.7 per cent. It was the sole complaint of 19 patients. Nausea and vomiting were present in 68.3 per cent of those patients with common duct stones.

Fever was present in 165 patients, or 12.1 per cent of the entire group. It was present in 32.1 per cent of those patients with acute or subacute cholecystitis and in 51, or 35.9 per cent, of the 142 patients with common duct stones. Fever was present in 16 patients with associated acute or chronic pancreatitis, in 11 patients with associated cholangitis or hepatitis and in 8 patients with an internal biliary fistula.

Jaundice was present or had been present according to the history in 255, or 18.8 per cent of the entire group. One hundred five patients were jaundiced at the time of operation.

Only 29 patients, or 2.1 per cent, had no symptoms referable to the biliary tract. Of these 29 patients, 4 were submitted to cholecystectomy because of a previous cholecystostomy. Four patients were found to have biliary calculi during laparotomy for other reasons and cholecystectomy was carried out. One patient had a cholecystectomy because he was a typhoid carrier. Twenty-five of the 29 patients without symptoms were found to have biliary calculi. One patient also had a common duct stone. Three were found on pathologic examination to have chronic cholecystitis and the remaining patient was one of the 2 patients in the entire group who had a normal gallbladder.

Abdominal tenderness on physical examination was present in 382 patients, or 28.2 per cent of the entire group. Abdominal tenderness was present in 60.6 per cent of those patients who had acute or subacute chronic cholecystitis.

Roentgenologic examination, either a flat film or a cholecystogram, was carried out in 1,172 patients. Cholelithiasis was reported in 926, or 79 per cent. Two hundred fifteen, or 18.3 per cent, showed a nonfunctioning gallbladder without visible calculi. One hundred ninety-one of these 215 patients were found at operation to have biliary calculi. Twenty-two patients were operated on in spite of normal x-ray findings and 10 were found to have stones in the gallbladder.

Comment. In this series, a considerably larger number of patients who were submitted to cholecystectomy were over 60 years of age, compared to the number of patients over 60 years in the 1942 to 1945 series reported by Adams and Stranahan. As Glenn (6) has pointed out, this increase in the number of patients in the older age groups who undergo cholecystectomy will inevitably have a bearing on the operative mortality. Certainly, the 52 patients over 70

years of age and the 6 patients over 80 years in this group indicate a need for earlier diagnosis and earlier surgical intervention in patients with disease of the biliary tract. In the earlier series, the proportion of females to males was approximately 3 to 1. In the present series it was approximately 2 to 1. As more patients are submitted to cholecystectomy because of the presence of stones without regard to severity of symptoms, sex distribution becomes more evenly balanced. In this respect, it is of interest to note that in autopsy studies Crump found the sex incidence of gallstones to be almost equal.

Although 9 out of 10 patients gave a history of pain, in many instances the pain was not characteristic of biliary tract disease. In many instances the pain and other symptoms were typical of the syndrome of irritable colon. Clinic experience has shown that the removal of disease of the biliary tract facilitates the successful treatment of the bowel symptoms in these patients. It also should be noted that the absence of pain does not rule out serious disease of the biliary tract.

Fever is not a common symptom of chronic cholecystitis and cholelithiasis and, when present, usually indicates a complication of cholelithiasis such as acute cholecystitis, common duct stones, pancreatitis, or hepatitis. Nausea and vomiting were also much more common in patients with common duct stones.

In spite of the fact that all patients who have evidence of cholelithiasis are advised to have cholecystectomy regardless of symptoms, it is of interest that only 2.1 per cent of this entire group were asymptomatic. We are inclined to agree with a statement made by Moynihan in 1910: "It is excessively rare for symptoms which are plain enough in their meaning if only we had the intelligence to recognize them, to be absent when stones lie within the gallbladder." Although 25 of the 29 patients who were asymptomatic were found to have stones in the gallbladder and only 1 patient showed no evidence of inflammation, it is likely that few of these patients would have remained asymptomatic had their gallbladders not been removed (Table II).

TABLE II.—SYMPTOMS OF CHOLECYSTITIS AND CHOLELITHIASIS: COMPARISON WITH PREVIOUSLY REPORTED STUDIES

	1942–1945		*1950–1953*	
	1,104 Patients		*1,356 Patients*	
Symptoms	*No.*	*Per cent*	*No.*	*Per cent*
Pain	1029	93.2	1187	87.5
Belching and flatulence	209	—	861	63.5
Nausea and vomiting	717	64.9	661	48.7
History of jaundice	200	18.1	255	18.8
Fever	—	—	165	12.1
No symptoms	26	2.3	29	2.1

As in the previous series, very few patients were found to have no calculi in the gallbladder after cholelithiasis had been indicated by roentgenologic examination, and approximately 90 per cent of the patients with nonfunctioning gallbladders on roentgenologic examination proved to have calculi at operation. A cholecystogram which is positive for calculi is a reliable indication of cholelithiasis. Calculi will usually be found in the patient who has persistent biliary symptoms and a nonfunctioning gallbladder on roentgenologic examination. A normal cholecystogram is unusual in patients with biliary calculi, but it does not rule out their presence.

OPERATIVE FINDINGS

The pathologic diagnosis in each instance has been based on histologic examination, and these are listed in Table III. A pathologic diagnosis of cholesterolosis of the gallbladder was made in 65 instances. In 59, stones were present in the gallbladder as well.

In addition to the changes in the gallbladder the following pathologic conditions were present: duodenal ulcer in 90 patients; gastric ulcer in 18; duodenal diverticula in 26; hiatal hernia in 62; diverticulosis of the colon in 115; diverticulitis involving the sigmoid colon in 7; an associated Meckel's diverticulum in 6; carcinoma of the stomach in 6; carcinoma of the colon in 17; associated hypertension in 66; arteriosclerotic heart disease in 53; diabetes in 46; and rheumatic heart disease in 11.

Forty-eight patients, or 3.5 per cent of the total group, had associated pancreatic disease. Five patients had a history or operative findings suggesting a previous episode of acute pancreatitis. Fifteen presented signs of acute pancreatitis at operation. In 28 patients there was evidence of chronic pancreatitis, including pancreaticolithiasis and pseudocysts of the pancreas. Ten patients had had previous pancreatic operations. Carcinoma of the pancreas was found in 3 patients and pancreatic cysts in 3 patients. Aberrant pancreas was found in the duodenum in 3 patients and in the stomach in 1 patient.

Thirty-three patients, or 2.4 per cent, showed evidence of cirrhosis of the liver. Five patients had cholangitis, 5 patients showed evidence of hepatitis on liver biopsy, and 5 patients showed only bile stasis on microscopic examination.

In addition to biliary calculi, 3 patients had associated papillomas of the gallbladder, and 4 patients had adenocarcinomas of the gallbladder, 1 of which appeared to arise in a diffuse polyposis of the gallbladder. Three patients had an associated papilloma of the ampulla of Vater.

Internal biliary fistulas were present in 20 patients, 3 of which were the result of previous operation. One patient had a cholecystocholedochal fistula, 2 patients had a cholecystocolic fistula, 9 had a cholecystoduodenal fistula, 4 had a choledochoduodenal fistula, and 1 patient had a fistula between the cystic duct and the duodenum. The 3 fistulas created by previous surgical procedures were between the gallbladder and the jejunum in one, gallbladder and duodenum in another, and the common duct and jejunum in the third.

Spasm or fibrosis of the sphincter of Oddi was present in 49 cases, an incidence of 3.6 per cent. Fifteen of these 49 patients had previously had a cholecystectomy. Twenty-six of these patients had jaundice or a history of jaundice; 11 of the 26 were jaundiced at operation and 15 gave a history of jaundice. Eleven of the patients in this group had associated common duct stones and 6 had acute or subacute cholecystitis. Patients operated on for common duct stricture were not included in this series except for 3 who had inflammatory strictures, 1 of which required plastic repair. Dilatation was considered sufficient in the other 2 cases.

Comment. Patients in whom the gallbladder showed subacute cholecystitis on pathologic examination usually presented the signs and symptoms of acute cholecystitis at operation and will be discussed under that heading. The fact that stones were not found in less than 5 per cent of the entire group indicates a reasonably small margin of error in the preoperative diagnosis of cholelithiasis. This figure is further reduced when one considers that 15 of these patients with chronic cholecystitis without stones had had a cholecystostomy previously for gallbladder disease. The frequency of disease of the biliary tract in this age group is shown by the number of patients found to have cholecystitis and cholelithiasis when they were operated upon for duodenal ulcer and other intra-abdominal pathologic conditions. The 2 patients who were operated on for gallbladder disease and in whom an unsuspected carcinoma of the colon was found emphasize again the importance of a routine abdominal exploration at the time of any laparotomy. The high incidence of associated pancreatic disease indicates the close relationship between pathologic conditions of the biliary tract and disease of the pancreas. The 4 patients who were found to have carcinoma of the gallbladder were operated upon for chronic cholecystitis and cholelithiasis, the carcinoma being an unexpected finding either at operation or on pathologic examination. All had associated gallstones and 1 patient also had multiple polyps of the gallbladder. Carcinoma of the gallbladder is rarely found unless biliary calculi are present, and this fact is another reason for removing the calculous gallbladder.

The number of spontaneous internal biliary fistulas involving the gallbladder and duodenum is an indication of the frequency

with which the duodenal wall may be involved by an inflammatory process in the gallbladder. The occurrence of fibrosis or spasm of the sphincter of Oddi in 49 patients indicates the frequency with which this condition may be present in patients with biliary tract disease.

TABLE III.—OPERATIVE FINDINGS ON 1,356 PATIENTS—1950–1953

Findings	*No.*	*Per cent*
Chronic cholecystitis with stones	1111	81.9
Chronic cholecystitis without stones	57	4.2
Subacute cholecystitis with stones	57	4.2
Subacute cholecystitis without stones	3	0.2
Acute cholecystitis with stones	68	5.0
Acute cholecystitis without stones	4	0.3
Normal gallbladder	2	0.1
Postcholecystectomy	54	4.0
Total	1356	

ACUTE CHOLECYSTITIS

In 72 patients (5.3 per cent) the pathologic report on the resected gallbladders was recorded as acute cholecystitis. In 8 of the 72 patients, pericholecystic disease in the form of perforation, abscess, and so forth, had occurred. In addition, 60 patients, or 4.4 per cent of the entire series, were reported to show subacute cholecystitis on pathologic examination. The preoperative findings were similar in both groups and at operation it was difficult to distinguish between them. Of the 132 patients with acute or subacute cholecystitis, the youngest was 19 years of age and the oldest 80 years of age. The average age was 55.1 years. There were 63 males and 69 females. Pain was present in 122, nausea and vomiting in 82, dyspepsia in 74, and fever in 52 patients. Jaundice was present in 32, abdominal tenderness in 79, and muscle guarding in 23 patients. Acute cholecystitis developed in 3 patients while they were convalescing from a laparotomy for unrelated disease.

Common duct stones were found in 32, or 24 per cent, of the patients with acute or subacute cholecystitis. Eight patients had associated acute pancreatitis and 5 patients had chronic pancreatitis. Fifteen patients had hepatitis, cholangitis, or cirrhosis of the liver. Six patients had fibrosis of the sphincter of Oddi and 7 had an associated internal biliary fistula. In 1 patient an acute gangrenous gallbladder was associated with carcinoma of the gallbladder; in 1 with a carcinoma of the pancreas, in 1 with a carcinoma of the bile duct, and in 1 with a carcinoma of the colon. Only 4 patients with acute cholecystitis and 3 patients with subacute cholecystitis did not have stones in the gallbladder. There was 1 instance of free perforation of the gallbladder with generalized peritonitis.

Comment. The fact that the incidence of acute or subacute inflammation in the gallbladder is almost 10 per cent, or twice that in the earlier series, reflects the increased frequency of early operation in cases of acute cholecystitis. The older age incidence of patients with acute cholecystitis and the fact that 1 patient was 80 years of age at the time of operation emphasize again the need for the elimination of disease of the biliary tract when it is first discovered. Although the incidence of females to males in the entire series was 2 to 1, it was approximately equal in patients with acute cholecystitis. The high incidence of pain, nausea, and vomiting, dyspepsia, fever, and tenderness is to be expected in acute cholecystitis. The facts that many of these patients were jaundiced and that an appreciable number were found to have associated stones in the common bile duct indicate the frequency with which pathologic changes in the common duct are associated with an acute inflammatory process in the gallbladder.

Although stones were not seen in 7 of the 132 patients, in many of these patients the gallbladder was emptied by suction before it was removed, and it is likely that most of the patients in this group with acute or subacute cholecystitis had associated biliary stones. The increase in associated pancreatitis is shown by the fact that approximately 10 per cent of the patients with acute or subacute cholecystitis had pancreatitis as compared to 3.5 per cent for the entire group, and is a reflection of the severity of the infectious process.

TABLE IV.—INDICATIONS FOR CHOLEDOCHOSTOMY: FREQUENCY AND RELATIVE IMPORTANCE, 498 PATIENTS—1950–1953

Indications	*No.*	*Per cent*	*Common duct stones found (142 cases)* — *No.*	*Per cent*
Thickened or dilated common duct	278	55.8	117	42.0
History of jaundice	208	41.8	90	43.2
Multiple small stones in gallbladder	167	33.5	42	25.1
Acute, subacute, or chronic pancreatitis	41	8.2	20	48.7
Noncalculous gallbladder with biliary tract symptoms	18	3.6	5	27.7
Positive or suspicious findings on palpation	10	2.0	10	100.0
Sediment in aspirated bile	5	1.0	1	20.0
Postcholecystectomy symptoms	62	12.4	23	37.1

COMMON DUCT STONES

One hundred forty-two patients, or 10.4 per cent of the entire group, were found to have stones in the common bile duct. Of the 1,104 patients reported in 1947, 16.8 per cent were found to have common duct stones. Exploration of the common duct was carried out in 498 cases, or 36.7 per cent, of the current series. Stones were found in 28.5 per cent of the ducts explored in this present series and in 36.7 per cent of the ducts explored in the earlier series. One hundred fourteen patients with stones in the gallbladder had associated common duct stones. Twenty-three patients who were found to have stones in the common duct had had a previous cholecystectomy. In 5 patients who had common duct stones, no stones were found in the gallbladder.

Sixty-two patients who had had a cholecystectomy previously had an exploration of the common duct. Five patients who were found to have common duct stones had had a cholecystectomy at the clinic, 2 of the 5 having been operated on before 1950.

Seventy-one patients, or 50 per cent, gave a history of recent weight loss. One hundred thirty patients (91.5 per cent) had abdominal pain, and 101, or 71 per cent, had typical biliary colic. Nausea and vomiting were present in 95, or 66.9 per cent, and fever was present in 51, or 35.9 per cent. Only 1 patient with common duct stones had no symptoms, although 12, or 8.5 per cent, did not have abdominal pain.

Ninety patients, or 63.4 per cent, were either jaundiced or gave a history of jaundice. Fifty-three patients were jaundiced at the time of operation and 37 gave a history of jaundice. Jaundice was present in 8 of the 12 patients who did not have pain. In the earlier series, 50 per cent of the patients with common duct stones were jaundiced or gave a history of jaundice. There were 255 patients in the entire series who were jaundiced or gave a history of jaundice. Ninety, or 35.3 per cent, of the 255 patients were found to have common duct stones. Fourteen patients who had acute cholecystitis had common duct stones, and 18 patients with subacute cholecystitis were found to have common duct stones. Thus 32 patients, or 24.2 per cent, who had acute or subacute cholecystitis had common duct stones. Eighty-seven patients, or 7.4 per cent, of those with chronic cholecystitis had common duct stones. Twenty-three, or 37.1 per cent, of the 62 patients with postcholecystectomy symptoms were found to have common duct stones.

The indications for exploration of the common duct are listed in Table IV.

In 26 patients with common duct stones, the duct was explored on the basis of a single indication. In 14 patients this indication was dilatation of the duct, while in 6 patients the finding of multiple small stones in the gallbladder and in 4 patients, jaundice, represented the only indications. Sediment in the aspirated bile was the sole indication for choledochostomy in 1 patient with common duct stones.

Thus, of the 142 patients with common duct stones, there was *one* indication for opening the common duct in 18.3 per cent (26 patients). In 67 patients, or 47.2 per cent, there were *two* indications for opening the duct. The most frequent combination was dilatation of the common duct and jaundice (36 patients). In the remaining 49 patients, *three or more* indications for choledochostomy were present. The most fre-

quent triple combination was jaundice, dilatation of the common duct, and multiple small stones in the gallbladder.

Comment. In spite of the fact that the same indications for common duct exploration existed through the years covered by this present series, there was a decrease in the number of common ducts explored, a decrease in the number of stones found, and a decrease in the percentage of stones found per duct explored. This would suggest an absolute decrease in the incidence of common duct stones in this present series. This present incidence of stones found in the common duct more closely approximates the figures reported by Walters, McLaughlin, Grove, Glenn (7) and Cole. This decrease in the incidence of common duct stones at the present time may reflect the wisdom of advising cholecystectomy in all cases in which a diagnosis of cholelithiasis has been made. The incidence (10.4 per cent) of common duct stones in this series is further decreased if the 23 patients who had had a previous cholecystectomy are excluded.

The fact that absence of stones in the gallbladder does not exclude the presence of stones in the common duct is demonstrated by the 5 patients who were found to have calculi in the common bile duct but none in the gallbladder. As pointed out in the previous study, weight loss is a common symptom in patients with common duct stones, the incidence being more than twice that for the entire group. Although the incidence of pain in patients with common duct stones was approximately the same as that for the entire group, the incidence of typical biliary colic was much more frequent in patients with common duct stones. Nausea and vomiting and fever were found much more frequently in the patients with common duct stones than in the patients making up the entire group.

Jaundice or the history of jaundice should always make one suspicious of the possible presence of a common duct stone. It should be remembered that common duct stones constitute only one type of common duct disease that may give rise to jaundice, since only 35.2 per cent of the patients with jaundice or a history of jaundice had stones (3). The presence of jaundice at the time of operation proved a more reliable indication of common duct stones since 50 per cent of the patients who were jaundiced had stones in the common duct, whereas only 24.6 per cent of patients who gave a history of jaundice were found to have stones in the common duct. The high incidence of common duct stones in patients who had previously had a cholecystectomy emphasizes again the need to consider the presence or absence of stones in the common duct at the time of every cholecystectomy. In spite of the fact that there is a tendency to omit exploration of the common duct in the presence of acute inflammation of the gallbladder, the same indications for common duct exploration should exist in these patients as in patients with chronic cholecystitis and cholelithiasis. Cattell (2) has listed acute cholecystitis as one of the indications for common duct exploration, and in this present series the percentage of common duct stones in patients with acute or subacute cholecystitis was 3 times the incidence of common duct stones in chronic cholecystitis.

The most frequent indications for choledochostomy in this series were jaundice, a dilated or thickened common duct, and multiple small calculi in the gallbladder. That these 3 indications are justifiable reasons for exploration of the common duct is shown by the fact that stones were found in 43.2 per cent of the patients whose common duct was explored for jaundice, in 42.0 per cent of those patients who had common duct exploration because of dilatation of the common duct, and in 25.1 per cent of those patients who had common duct explorations because of multiple small stones in the gallbladder. Although definite palpation of a stone in the common duct is always an absolute indication for common duct exploration, the incidence of this indication could not be accurately determined from a review of the operative record. It was also

obvious from the percentages given that the majority of patients had a combination of these indications for choledochostomy. It is of interest that of the 26 patients with common duct stones in whom only 1 indication was present, multiple small stones in the gallbladder were the only indication for opening the common duct in 6 patients. In our experience, although small stones in the gallbladder proved less reliable than dilatation or jaundice as an indication for common duct exploration, it occasionally may be the only indication that common duct stones are present.

PREVIOUS BILIARY TRACT SURGERY

A total of 109 patients had previously had surgical procedures on the biliary tract; 84 had had 1 operation, 21 had had 2 operations, and 4 had had 3 or more operations. Fifty-one patients had had a cholecystostomy; 54 had had a cholecystectomy, 14 of whom had also had choledochostomy; 17 patients had had a choledochostomy alone; 5 patients had had a cholecystostomy and choledochostomy. In addition to the 54 postcholecystectomy patients who had had a cholecystectomy and were referred to the clinic, 8 patients had previously had a cholecystectomy at the clinic during this period, making a total of 62.

In these 62 patients who were operated upon because of symptoms persisting after a cholecystectomy, 23 were found to have common duct stones. A portion of the gallbladder or a long cystic duct was found in 31, in 16 of whom stones were present in the gallbladder or remnant of the cystic duct. Fifteen patients had spasm or fibrosis of the sphincter of Oddi, 7 had acute or chronic pancreatitis, 6 had cholangitis, hepatitis, or cirrhosis, 3 had a choledochoduodenal fistula, and in 2 patients adhesions between the duodenum and colon and the gallbladder bed constituted the only finding.

Of the 48 patients whose only previous surgical procedure had been a cholecystostomy, 3 were found to have acute cholecystitis with stones; 3 subacute cholecystitis with stones, 28 chronic cholecystitis with stones, and in 14 patients chronic cholecystitis without stones was present. Common duct stones were present in 12, cirrhosis or hepatitis was found in 7, pancreatitis in 4, common or hepatic duct stricture in 2, an external biliary fistula was present in 6, fibrosis of the sphincter of Oddi was present in 7, and in 1 a cholecystoduodenal fistula had developed.

Comment. The large number of patients who had had previous biliary tract surgery is an indication of the frequency with which secondary operations are necessary in patients with biliary tract disease. Granted that in many of the patients who had had a previous cholecystostomy, further surgery at the time of the original operation might have been unduly hazardous, it should be remembered that cholecystostomy in itself is an incomplete operation and that a second and more definitive procedure will be necessary in almost all of these patients. The fact that pathologic changes in the biliary tract are all too often missed, even following a so-called definitive procedure, is indicated by the fact that in only 2 of the 62 postcholecystectomy patients, no biliary tract disease was found at the second operation. These 2 patients were found to have extensive adhesions between the duodenum, colon, and the gallbladder bed. Thirty-nine of these patients had stones remaining in a remnant of the gallbladder or the cystic duct, or in the common bile duct. Whenever possible, patients with cholecystitis and cholelithiasis should have a cholecystectomy, removing all of the gallbladder and all but a small portion of the cystic duct, as well as a choledochostomy if indicated. This can be done and injury to the common duct is not likely to occur if the ampulla of the gallbladder is carefully reflected from the common hepatic duct and the junction of the cystic and common ducts is accurately visualized before a clamp is placed on the cystic duct. Moreover, unless the common bile duct is clearly exposed and the size of the duct determined, the indications for

choledochostomy cannot be properly assessed. Dilatation of the common duct was the only indication for exploration of the duct in 14 patients with common duct stones.

OPERATIVE PROCEDURES

Thirteen hundred and sixty-four operations were performed on 1,356 patients. These operative procedures are listed in Table V. A number of patients, in addition to cholecystectomy, had associated operative procedures on the biliary tract, such as duodenotomy or sphincterotomy. A small number had partial pancreatectomy or excision of aberrant pancreas or choledochal cyst. Five hundred and twenty-three patients, or 38.5 per cent, had an appendectomy and 37 had subtotal gastrectomy in addition to cholecystectomy. In addition to cholecystectomy, 25 patients had resection of the small or large bowel, 21 had an associated hernial repair, and 21 had an associated gynecologic procedure. Numerous other procedures unrelated to the biliary tract were also performed.

Comment. The low incidence of cholecystostomy is partly due to the fact that fewer patients with acute disease of the biliary tract are referred to the clinic, but it also illustrates our belief that, whenever possible, definitive surgical procedures on the biliary tract should be done.

The patients who had choledochostomy in addition to cholecystectomy have previously been discussed. The 62 patients who had choledochostomy following a previous cholecystectomy represent the patients who were not relieved by their primary procedure. Thirty-nine patients had duodenotomy in addition to cholecystectomy to determine the patency of the lower end of the common duct and for inspection of the ampullary area. We do not hesitate to open the duodenum whenever there is any question regarding patency of the lower end of the common duct. If sphincterotomy is indicated, it is always done under direct vision. Our concern over the importance of maintaining a patent ampulla is indicated by the fact that 103 patients had implantation of a long arm T tube extending through the ampullary area into the duodenum.

TABLE V.—TYPES OF BILIARY TRACT PROCEDURE, 1,356 PATIENTS—1950–1953

Procedure	*No.*	*Per cent*
Cholecystectomy	859	62.9
Cholecystectomy and choledochostomy	435	31.8
Choledochostomy with or without excision of gallbladder or cystic duct remnant	63	4.6
Cholecystostomy	6	0.4
Liver biopsy alone	1	0.1
Total procedures	1364	

The incidence of appendectomy in addition to cholecystectomy (38.5 per cent) is approximately the same as in the previously reported series. We remove the appendix unless we believe it will unduly extend the operative procedure. The number of resections of the stomach and colon is indicative of the pathologic changes to be expected in patients of this age group. These patients were being operated upon for their colon or gastric lesion. Routine abdominal exploration is carried out at the time of any laparotomy. If stones are found in the gallbladder, cholecystectomy not infrequently is carried out in addition to the primary operative procedure. It is, however, a decision that should not be made lightly, as will be seen in the analysis of the mortality figures.

COMPLICATIONS

Atelectasis occurred in 18 patients; pneumonia in 6; pulmonary embolism in 6; pleural effusion in 2, and acute pulmonary edema in 1. A cerebrovascular accident occurred in 3 patients; coronary occlusion in 1; thrombophlebitis or phlebothrombosis in 23, and peripheral arterial emboli in 1.

Wound infection occurred in 28 patients; wound dehiscence in 13; incisional hernia in 3; and hematoma in 1.

Eight patients required re-exploration of the common duct. Three patients had retained stones, 1 fibrosis of the sphincter of Oddi; 1 sclerosing cholangitis; 1 carcinoma of the bile duct; 1 was reoperated upon for a dislodged T tube; and 1 was re-explored because of evidence of common duct stones

TABLE VI.—ANALYSIS OF 16 DEATHS FOLLOWING SURGERY—1950–1953

Case	*Age and sex*	*Previous operation*	*Jaundice*	*Operation*	*Cause of death*	*Autopsy*
				ACUTE CHOLECYSTITIS		
1	58 M	Subtotal gastrectomy	Yes	Cholecystectomy and drainage of pancreatic abscess	Pancreatic necrosis and subphrenic abscesses on 9th day after operation	No
2	65 F	No	Yes	Cholecystectomy, choledochostomy, transduodenal sphincterotomy	Cerebrovascular accident with hemiplegia and coma on 5th day after operation	No
				CHRONIC CHOLECYSTITIS		
3	67 M	No	No	Subtotal gastrectomy, cholecystectomy	Generalized peritonitis secondary to leak from duodenal stump on 8th day after operation	Yes
4	57 F	No	No	Splenectomy, cholecystectomy	Intra-abdominal hemorrhage, blood dyscrasia on 4th day after operation	Yes
5	60 F	No	No	Cholecystectomy, choledochostomy	Subphrenic and retroperitoneal abscesses and cortical necrosis of kidneys on 38th day after operation	Yes
6	51 M	No	No	Hemicolectomy, cholecystectomy	Multiple peripheral arterial emboli, rheumatic heart disease on 6th postoperative day	No
7	55 M	No	Yes	Cholecystectomy, choledochostomy, transduodenal sphincterotomy	Cirrhosis of liver with hepatorenal failure 13 days after operation	Yes
8	78 M	No	Yes	Cholecystectomy, choledochostomy, transduodenal sphincterotomy	Hepatorenal failure with bile stasis, bronchopneumonia on 10th day after operation	Yes
9	59 M	No	No	Subtotal gastric resection, cholecystectomy	Bronchopneumonia 6 days after operation	No
10	50 M	Cholecystostomy	Yes	Cholecystectomy, choledochostomy, duodenotomy	Duodenal fistula, pancreatitis, acute and chronic, on 31st postoperative day	Yes
11	60 M	No	No	Cholecystectomy, excision of duodenal diverticulum	Pancreatic necrosis, pulmonary emboli, subphrenic abscess on 55th postoperative day	Yes
12	53 F	No	No	Cholecystectomy	Acute massive liver necrosis secondary to streptococcal septicemia 3 days after operation	Yes
13	77 F	No	No	Cholecystectomy	Hypertensive cardiovascular disease with uremia and renal failure 10 days after operation	No
				BILIARY PROCEDURES FOLLOWING CHOLECYSTECTOMY		
14	62 F	Cholecystectomy	Yes	Choledochostomy	Cholangitis, marked multiple liver abscesses, staphylococcal septicemia 81 days after operation	Yes
15	73 F	Cholecystectomy, choledochostomy	Yes	Choledochostomy	Cerebrovascular accident with hemiplegia and coma 4 days after operation	No
16	61 M	Cholecystectomy, choledochostomy	Yes	Choledochostomy	Myocardial infarction, biliary fistula on 1st day after operation	Yes

in the postoperative cholangiogram. Three patients had intestinal obstruction necessitating surgical relief; in 5 patients acute pancreatitis developed during the postoperative period; 4 patients had a temporary cutaneous fistula, and 7 patients developed subphrenic abscesses.

Comment. The incidence of pulmonary and cerebrovascular complications remains approximately the same as in the 1942 to 1945 series. This may be expected since the present series includes an even higher number of patients over 60 years of age. In spite of the increased use of the antibiotics, there has been no decrease in incidence of wound infection or of subphrenic abscess. The fact that 13 had dehiscence of the wound indicates the need for careful wound closure. These patients are usually obese, are frequently elderly, and often have extensive disease of the biliary tract. Fortunately, none of the patients with dehiscence died.

The fact that only 3 of the 1,356 patients in this series required reoperation for common duct stones (as of December 1953) indicates that every effort was made to carry out a definitive procedure at the initial operation in each of these patients.

MORTALITY

There were 16 deaths in the 1,356 patients who had 1,364 operations, or a mortality of 1.1 per cent. Seven of 327 patients over the age of 60 died following the operative procedure, a mortality of 2.1 per cent. Eight, or 50 per cent, of the deaths occurred in patients who were jaundiced at the time of operation.

There were 3 deaths in the 62 patients who had had a previous cholecystectomy, or a mortality of 4.8 per cent. In the group of patients with acute or subacute cholecystitis (132 cases) there were 2 deaths, a mortality of 1.5 per cent; and in the group of patients with chronic cholecystitis and cholelithiasis (1,168 cases) there were 11 deaths, or a mortality of 0.9 per cent.

Five deaths followed cholecystectomy and choledochostomy, giving a mortality of 1.1 per cent for the 435 patients who had both procedures. Eight deaths followed cholecystectomy alone (859 cases), a mortality rate for this procedure of 0.9 per cent, and the remaining 3 patients died following choledochostomy with or without excision of the gallbladder remnant or cystic duct stump.

The causes of death in the 16 patients are listed in Table VI.

Comment. It is of interest that the mortality of patients over 60 years of age was almost double the over-all mortality. The effect of the complications of gallbladder disease as well as of age is shown by the fact that 50 per cent of all deaths occurred in patients who were jaundiced at the time of operation. Five of the deaths occurred in patients who had an additional major abdominal procedure at the time of their cholecystectomy. Usually this was done in an effort to save elderly patients the possible need for a second abdominal operation. It means, however, that the operative risk must be carefully evaluated before cholecystectomy is combined with another major abdominal procedure. The mortality of cholecystectomy plus choledochostomy is more than that for patients who have cholecystectomy alone, but is to be expected in view of the additional pathologic changes present. Persistent disease of the common duct definitely increases the mortality rate in biliary tract disease as shown by the 4.8 per cent mortality in the postcholecystectomy group. Although the mortality in the patients with acute and subacute cholecystitis was slightly higher than the overall mortality, only 1 of the 2 deaths, namely, that from acute pancreatic necrosis, could be related to the inflammatory process in the gallbladder. The cause of death in 7 of the 16 patients was entirely unrelated to the pathologic changes in the biliary tract and indicates the risk inherent in operating upon patients in this age group. The cause of death in 3 of the remaining 9 patients was pancreatitis, a complication seen not infrequently after other upper abdominal procedures. Of the remaining 6 deaths, 4 were primarily hepatic in origin and 2 were the result of overwhelming infection.

SUMMARY AND CONCLUSIONS

The clinical records of 1,356 patients who were operated upon for cholecystitis and cholelithiasis during the 4 year period between 1949 and 1954 have been reviewed.

All but a few patients with biliary calculi will have some symptoms of their disease. A careful history plus the use of the cholecystogram presents an accurate means of making the diagnosis in these patients.

An increasing number of patients over 60 years of age are being operated upon for cholelithiasis. Acute cholecystitis and common duct stones, the major complications of cholelithiasis, occur more frequently in patients over 60, and they frequently coexist.

A definitive operation for patients with cholelithiasis can be done only by an ac-

curate demonstration of the cystic duct and its junction with the common duct. Careful exposure of the common duct is necessary to evaluate the need for choledochostomy and should result in fewer rather than more common duct injuries.

The mortality for the entire group was 1.1 per cent. The mortality for the patients having surgical procedures on only the biliary tract, not excluding appendectomy, was 0.8 per cent. The principal factors responsible for this mortality were the relatively large number of patients over 60 years of age, extensive disease of the biliary tract as indicated by the presence of jaundice, and the number of patients requiring secondary operations upon the biliary tract. If, in most instances, patients with cholelithiasis were advised to have a cholecystectomy (with choledochostomy when indicated) when their stones are discovered, before complications have developed and before they enter the older age groups, the mortality and the morbidity of biliary tract disease would be improved.

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THE USE OF STREPTOCOCCAL ENZYMES IN THE IMMEDIATE CLOSURE OF CONTAMINATED INCISIONS

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THIS STUDY WAS UNDERTAKEN to determine if instillation of streptokinase and streptodornase into infected, grossly or potentially contaminated incisions would permit immediate closure of these wounds which would probably not otherwise be closed. It is known that streptokinase and streptodornase (SK-SD) exert their maximal débriding effects in fresh infections, abscesses, and hematomas because of the specificity of the enzyme-substrate relationships involved, streptokinase being effective only for the lysis of fibrin, and streptodornase being effective for depolymerization of the desoxyribonucleoprotein fraction of purulent exudate.

If streptokinase and streptodornase are particularly effective in the débridement of fresh lesions, it would appear that extending their use in a prophylactic manner to grossly contaminated wounds might be of value in preventing infection. The potential success of this use is based on the premise that instillation of these proteolytic substances into a closed contaminated incision produces lysis of fibrin and necrotic tissue and purulent exudate as formed by bacterial action. In addition, as a result of the irritative action of the enzymes, an increased influx of serum carries phagocytes, parenterally administered antibiotic or chemotherapeutic agents, possibly humoral antibodies, and catalytics necessary for enzyme activation, into the interstices of the closed area. Johnson has studied the cytologic effects of local injections of SK-SD into patients, and noted that their introduction into areas of inflammatory exudation was followed by an outpouring of living polymorphonuclear leucocytes reaching a maximum in 24 hours. Changes in the local cytologic pattern was characterized by a marked decrease in degenerating and degenerated cellular forms along with this rapid rise in leucocytes. This instillation also achieved depolymerization of desoxyribonucleic acid by streptococcal desoxyribonuclease (streptodornase) and dispersed the clumped leucocytes, the conglomeration of which was apparently attributable to a matrix of desoxyribonucleoprotein.

By the use of Feulgen stain methods, Johnson determined that living cells were unaffected by the enzymes. Following enzymatic lysis of the bacterial substrate, the bacteria are destroyed and infection arrested at its inception. Adequate drainage for the removal of lysed products must be afforded through a small opening in the incision. Results obtained in this clinical investigation indicate the possible validity of this concept.

CASE STUDIES

Following is a list of the varying types of surgical conditions (73 cases) in which SK-SD instillation was used in conjunction with immediate closure, except for drainage defects: appendectomy for gangrenous or ruptured appendices in 18 patients; operations on the colon in 10; excision of draining sinuses in 10; posterior wounds following abdominoperineal resections in 12; infected amputation stumps in 3; cholecystectomy incisions in 2; secondary closure of infected wounds in 6; and deep abscesses in 12 patients.

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APPENDECTOMY FOR GANGRENOUS OR RUPTURED APPENDICES

No method of treatment or drainage ordinarily used is capable of forestalling wound infection in all cases of appendectomy for gangrenous appendicitis, gangrenous appendicitis with rupture on removal, or gangrenous appendicitis with rupture and abscess. The incisions in these cases are therefore considered ideal for a trial study of SK-SD instillation for preventing postoperative infection.

The establishment of adequate controls for an investigation of this nature does not fulfill rigid requirements. The use of control solutions of saline, antibiotics, or chlorinated agents was not employed largely because of the limited number of cases available for the study. Instead, the incidence of wound infection following a large number of appendectomies, in which current methods of management were used, was determined. This is believed to be acceptable as a control measure.

Incidence of wound infection in appendectomy incisions. In order to learn the incidence of infection in appendectomy incisions in this hospital, the charts of all patients operated upon for appendicitis between November 1947 and March 1954 at Wadsworth Hospital were reviewed. The total group was subdivided into those in which the appendix was described as ruptured and those in which it was not ruptured, and the incidence of wound infection determined for each. During the 6½ year period covered, antibiotics were used routinely. In the ruptured group, 39 out of 81 patients (48 per cent) developed wound infections. In the unruptured group of 1,254 patients, 101 (8 per cent) manifested this complication.

Influence of drainage procedure on incidence of infection in appendectomy incisions. Since the method of drainage measurably affects the incidence of wound infection following appendectomy, particularly in the case of the ruptured appendix, these date have also been determined and correlated with the incidence of infection: Wound infection developed in 11 cases (84.5 per cent) of 13 in which no drain was used, in 12 cases (55 per cent) of 22 in which a subcutaneous drain was used, and in 16 cases (35 per cent) of 46 in which subcutaneous and intraperitoneal drains were used. A decreased incidence of wound infection occurred as more drainage was used, indicating the superiority of both subcutaneous and intraperitoneal drainage over subcutaneous drainage alone. Determination of the role of drainage is considered important to this study because it is likely that the results obtained by instillation of SK-SD are due to some extent to improved drainage.

Materials and methods. Closure of the appendectomy incisions was performed as follows: The peritoneum, muscle layers, and fascia were closed in the usual manner with running or interrupted chromic catgut. A No. 16 or No. 18 polyethylene tube and small Penrose drain were laid in the subcutaneous fat overlying the fascia and the subcutaneous tissue approximated with fine chromic sutures. Skin closure was then done with silk sutures or clips, leaving a short aperture at the dependent or lateral end for drainage. In the earlier cases, a second polyethylene tube was introduced through the fascia layer down to the transversus fascia. This was later found to be unnecessary, since one tube into the fat was found to be adequate to prevent infection. Contact for 4 to 6 hours between enzyme solution and the interstices of the closed incisions is of great importance, as is complete drainage of the solution and its lysed products following the period of contact. Initially, the enzyme solution was instilled through the tube leading in through the least dependent or medial end of the incision, but it was found that occasionally inadequate drainage occurred and the enzyme solution caused a cellulitis of the undrained flank tissues. To prevent this, the patient was placed with his right side up and the solution instilled through the lateral or dependent end.

SK-SD instillation, in concentrations of 10,000 units of SK and 2,500 units of SD

TABLE I.—APPENDECTOMY INCISIONS TREATED WITH SK-SD

Case No. Patient Age, yrs.	*Status of appendix*	*Culture*	*Antibiotic*	*Appendectomy*	*Subcut. drain*	*Peritoneal drain*	*SK-SD, days*	*Healing of incision*
1 A.K. 33	Gangrenous. Recent rupture	Strep. gram neg. rods	+	+	+	0	8	+
2 M.W. 40	Ruptured 10 days. Pelvic abscess. Ileal obstruction	A. Aerog.	+	+	+	+	5	+
3 S.B. 63	Ruptured. Peritonitis. Diabetes	E. coli	+	+	+	+	3	Superficial suppuration
4 K.M. 65	Ruptured. Pericecal abscess	E. coli	+	+	+	+	7	+
5 J.I. 29	Ruptured on excision	Not done	+	+	+	+	7	Developed pelvic abscess +
6 A.M. 66	Ruptured on excision	E. coli	+	+	+	0	4	+
7 A.B. 58	Ruptured on excision	E. coli	+	+	+	0	12	+
8 T.D. 32	Ruptured on excision	E. coli	+	+	+	+	10	Sterile cellulitis +
9 R.K. 42	Gangrenous	Not done	+	+	+	0	7	+
10 G.S. 31	Gangrenous pericecal peritonitis	E. coli	0	+	0	0	6	Small subcutaneous suppuration. E. coli
11 I.D. 31	Ruptured. Pericecal abscess	E. coli	+	+	+	+	7	+
12 E.M. 24	Ruptured	E. coli	+	+	+	0	7	Small subcutaneous collection of sterile fluid
13 C.N. 41	Ruptured peritonitis	Not done	+	+	+	0	5	Slight sterile cellulitis
14 F.T. 33	Ruptured. Large omental abscess	No growth	+	+	+	+	5	+
15 R.W. 44	Ruptured. Pericecal abscess	E. coli	+	+	+	+	7	+
16 E.D. 30	Gangrenous. Pelvic postop. jejunal obstruction and large abscess.	E. coli	+	0	+	+	4	+
17 D.H. 20	Ruptured	E. coli	+	+	+	+	7	+
18 O.L. 58	Ruptured. Pericecal abscess	E. coli	+	+	+	+	7	+

per cubic milliliter, was used once daily for periods of 4 to 6 hours. Instillation was done once daily for from 3 to 12 days, but an average of 5 to 7 days was usually considered adequate. As mentioned before, one tube introduced into the fat along with a small Penrose drain is considered adequate if good contact and drainage is achieved.

Results. Data relative to 18 cases of appendectomy with contamination of the incisions are presented in Table I. In 13 of these, significant massive contamination of

TABLE II.—OPERATIONS ON THE COLON

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Bowel Prep.*	*Antibiotic*	*Treatment*	*SK-SD days*	*Healing of Incision*
1 W.H. 46	Amebic granuloma. Perforated	Neg.	+	+	Resection of transverse colon and granuloma	6	+
2 C.L. 55	Polyp of splenic flexure	Gram neg. bacilli, cocci	+	+	2 colotomies. Scoping of transverse and left colon	7	Small subcut. collection of sterile fluid
3 A.M. 57	Polyp of sigmoid	Not done	+	+	Colotomy, polypectomy	7	+
4 J.P. 65	Diverticulitis with perforation. Subhepatic abscess	Hem. Staph. albus, E. coli	0	+	Partial colectomy. Transverse colostomy. I & D subhepatic abscess	7	+
5 E.W. 57	Diverticulitis transverse colostomy	E. coli	+	+	Closure of colostomy. Anterior sigmoid resection	6	+
6 D.B. 48	Ca. ascending colon. Peri-inflammation cecum perforated	Paracolon b, E. coli, Klebsiella	0	+	Intraperitoneal drainage	10	+
7 J.H. 60	Ca. of rectum with obstruction of ileum. Perforation of bowel	E. coli	0	+	Transverse colostomy closure, bowel perf.	8	+
8 A.R. 64	Sigmoid polyp	E. coli	+	+	Colotomy. Scoping of right colon	5	+
9 E.Z. 41	Ca. of rectum metastatic to liver	Hem. Staph albus	+	+	Abdominoperineal resection. Colon perforated	7	P.O. hematoma wound separation. Secondary closure
10 F.G. 41	Posttraumatic stenosis of sigmoid	No growth	+	+	Colotomy. Scoping of sigmoid. Resection of stenosed area	7	+

the incisions from abscess or peritonitis was observed. In 4 cases contamination resulted from perforation of the appendix on removal and in 1 from a gangrenous appendix. Had ordinary methods of management been utilized it seems likely that significant infection would have resulted in several of these 18 incisions. With the use of enzyme instillation uneventful healing was obtained in 16. Suppuration occurred superficially in the wound of Patient 3, a 63 year old male diabetic with hepatic cirrhosis who had a ruptured appendix and marked localized peritonitis. This patient pulled his tubes and drain out after only 3 days of enzyme instillation and these were not replaced. It is believed that had this patient had 7 days of treatment, primary healing may have taken place. Suppuration also occurred in the incision of Patient 10. Here no drainage was afforded around the polyethylene tube, but once this was provided, healing was rapid. Inadequate drainage will cause a sterile chemical cellulitis to form in the cutaneous tissue of the closed wounds, as occurred in Patients 8 and 13. Poor drainage may also cause small superficial collections of sterile serous fluid to form as in Patient 12. Careful attention to free drainage following the contact period will prevent these minor complications.

Suppuration only occurred in Patient 10 in whose case neither subcutaneous nor intraperitoneal drainage, other than around the polyethylene tube, was afforded, and in Patient 3 just described, in whose case enzyme treatment was used for only 3 days. Thus, healing occurred in all 6 patients who had subcutaneous drainage alone, and in 10 out of 11 who had combined subcutaneous and intraperitoneal drainage. Absorbable suture was used in all closures and intraperitoneal drainage was achieved through a stab wound lateral to the contaminated appendectomy incisions. The intraperitoneal drains were gradually removed, usually in

5 to 7 days or when drainage became serosanguineous.

The combination of subcutaneous and intraperitoneal drainage was used in 11 out of 18 patients. Indications for intraperitoneal drainage were: (1) localized abscess in 7 cases, (2) residual necrotic tissue and gross contamination from perforation of the appendix at the time of removal in 3 patients, and (3) residual necrotic tissue and peritonitis from rupture of the appendix in 1 patient. One, Patient 5, developed a pelvic abscess following removal of the intraperitoneal drain. No complications resulted from intraperitoneal rubber drains in any of the 11 patients. Stab wound, rather than transincisional intraperitoneal drainage, was employed in this series in order to divert drainage away from the incision being treated with enzymes.

At the present time most surgeons elect to drain intraperitoneally when abscess is present, stump closure is insecure, or the source of infection or contamination remains. The majority do not employ such drainage when contamination has resulted from the surgical procedure. In this small series such drainage was employed in the latter category when significant fecal contamination of the right gutter and wound resulted from perforation of the appendix at the time of removal. Whether this is necessary in order to obtain the same results would have to be determined by a larger number of cases controlling this factor. Supporting this more liberal use of intraperitoneal drainage is an analysis by Fowler and Bollinger of 7 deaths in a series of 1,816 cases of nonperforated acute appendicitis. They point out that 5 of these deaths could probably have been prevented by draining the cecal region. It would appear that the choice of intraperitoneal drainage should depend on the extent of bacterial contamination which has resulted intraperitoneally rather than the status of the appendix. If gross fecal contamination has occurred, and especially if there is some residual necrotic tissue, it would appear wise to drain to that point. This measure applies particularly to older patients and to those with concomitant disease such as diabetes. Insecure intestinal closure and definite abscess cavity are, of course, positive indications for intraperitoneal drainage.

Based on the results obtained in this small series, the following regimen for grossly contaminated incisions resulting from acute appendicitis is suggested: (1) immediate closure of the incision with a Penrose drain and a polyethylene tube inserted into the subcutaneous fat for drainage and instillation of SK-SD, (2) intraperitoneal drainage through a stab wound if gross contamination of the appendiceal region or localized abscess has been encountered, (3) appropriate antibiotic therapy. The usual measures such as carefully protecting the wound edges with laparotomy pads, irrigation of the incision before closure, careful hemostasis and tissue handling, and closure without tension should, of course, be observed.

OPERATION ON THE COLON

SK-SD were used in the abdominal incisions of 10 patients who had undergone large bowel surgery complicated by observed fecal contamination of the peritoneal cavity and incision. The data on these patients are summarized in Table II. The method of closure was similar in all respects to that employed in the appendectomy series previously described. The concentration of enzyme solution used, the contact period, and the positioning of the patient were essentially the same.

Bowel preparation by antibiotic and mechanical means was done preoperatively in 7 of the 10 patients. Positive cultures of pathogenic enteric organisms were obtained in 4 of these patients indicating the unreliability of bowel preparation at least in our hands. In 3 patients having emergency surgery and no bowel preparation, positive cultures were returned. The interior of the bowel was examined by colotomy and sigmoidoscopy in 3 patients, which resulted in inevitable spillage of bowel contents.

TABLE III.—EXCISION OF DRAINING SINUSES AND CLOSURE

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Antibiotic*	*Treatment*	*SK-SD days*	*Healing*
1 E.V. 65	Groin abscess. P.O. hernioplasty	Hem. staph. aureus	+	I & D. Removal of sutures	7	+
2 M.P. 45	Groin abscess. P.O. hernioplasty	Hem. staph. aureus	+	Excision of sinus and sutures	7	+
3 B.G. 54	Chronic sinus to gallbladder bed	—	+	Excision of sinus and silk sutures	10	+
4 H.H. 54	Ileal cutaneous fistula	Proteus gram cocci	+	Segment of ileum and sinus excised	7	+
5 R.T. 32	Abdominal wall granuloma and sinus ulcerative colitis	Microaerophilic strep.	+	Sinus excised	6	Superficial suppuration
6 E.K. 55	Abdominal wall suture granuloma	—	+	Excision of infected granuloma	7	+
7 S.O. 49	Infected hernia incision, tantalum mesh	—	+	Excision of tantalum mesh	12	+
8 R.H. 30	Shrapnel abscess in pelvic wall	E. coli, paracolon B.	+	Excision of shrapnel and sinus	4	+
9 B.S. 43	Recurrent shrapnel abscess, arm	No growth	+	Shrapnel excised	4	+
10 R.S. 25	Shrapnel abscess rhomboid muscle	—	+	Shrapnel excised	7	+

Uneventful healing of the incisions occurred in 8 of the 10 patients. In Patient 2 (Table II) a small subcutaneous collection of sterile fluid was noted in the incision but healing was not significantly delayed. This method was considered a failure in the case of Patient 9 whose wound separation occurred secondarily to hematoma and infection. The infected wound was closed secondarily and SK-SD were instilled for 9 days. Healing was slow but progressive.

EXCISION OF DRAINING SINUSES AND CLOSURE

Ten patients with chronically infected draining sinuses were subjected to excision of the sinuses and removal of any foreign bodies responsible for the purulent drainage. Closure of the wounds was then performed and SK-SD were instilled in the manner described. Data on these patients are summarized in Table III.

It is well known that following the removal of a foreign body, a wound may heal rapidly, especially if aided by drainage. In the 10 cases presented here, it is believed that the SK-SD instillation aided in achieving the uniformly successful healing of the wounds in all the patients. Patient 7 had severe cellulitis, edema, and infection about the tantalum mesh in the groin. Closure of this tissue, following the removal of the mesh, seemed only to invite trouble. Healing was rapid, however. The groin abscesses in Patients 2 and 4 were recently postoperative. Following incision and drainage of this lesion, ordinary procedure would have been to leave the incisions open to heal in from the base or to be closed secondarily after the infection had been treated intensively with compresses. Immediate closure was successful in both.

CLOSURE OF POSTERIOR WOUNDS FOLLOWING ABDOMINOPERINEAL RESECTIONS

In June 1952 Beahrs and Jordan published their experiences with the instillation

TABLE IV.—POSTERIOR WOUNDS OF ABDOMINOPERINEAL RESECTION, CLOSURE

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Postop. antibiotics*	*Treatment*	*SK-SD days*	*Approx. healing in weeks*
1 L.A. 55	Ulcerative colitis	—	+	Abdominoperineal resection	3	Bleeding @ 3 days (see text)
2 M.W. 32	Ulcerative colitis	—	+	Abdominoperineal resection	7	3
3 L.K. 30	Ulcerative colitis	Enterococci	+	Abdominoperineal resection	7	3
4 M.S. 32	Ulcerative colitis	E. coli	+	Proctectomy	5	2
5 E.A. 51	Ulcerative colitis Diabetes	Proteus staph. aureus	+	+	1	6 mo.
6 C.G. 61	Ca. of rectum	—	+	Abdominoperineal resection	9	2
7 J.C. 58	Ca. of rectum	—	+	Abdominoperineal resection	3 q.o.d.	3
8 L.M. 69	Ca. of rectum	—	+	Abdominoperineal resection	7	7
9 W.R 60	Ca. of rectum	—	+	Abdominoperineal resection	7	3
10 F.O. 60	Ca. of rectum	—	+	Abdominoperineal resection	7	4
11 E.Z. 41	Ca. of rectum	—	+	Abdominoperineal resection	7	3
12 E.C. 63	Ca. of rectum	—	+	Abdominoperineal resection	5	4

of SK-SD into primarily closed posterior wounds of abdominoperineal resections in a small series of patients. They found that the method permitted primary closure, except for a drainage aperture, and resulted in earlier healing. We have made a nearly identical study in 12 patients and obtained similar results. In the cases selected for this series good peritonealization of the floor of the pelvis was achieved. The levator muscles were apposed with No. 00 chromic catgut as was all other tissue which could be brought together. The skin was then closed, leaving a defect open anteriorly through which polyethylene tubes and Penrose drains were led. Apposition of the levator muscles converted the defect into upper and lower compartments. A polyethylene tube and Penrose drain were thus introduced into each space. Two vials of varidase® were dissolved in 40 milliliters of saline and instilled into the defect once daily. The patient was positioned on his back for 6 hours and thereafter turned on his side or stomach or allowed up for free drainage. Data on the patients treated are summarized in Table IV.

Healing was uniformly good in all 12 cases and, on the average, the perineal defects were nearly healed approximately 3 weeks after operation. These results compare with those obtained by Beahrs and Jordan, and the method is believed to be of aid in the handling of the perineal defects. Following discontinuance of enzyme instillation, the tubes were removed and the closing defect irrigated once daily with saline solution. No instances of suppuration occurred previous to complete healing.

TABLE V.—INFECTED AMPUTATION STUMPS, REVISION AND CLOSURE

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Antibiotic*	*Treatment*	*SK-SD, days*	*Healing*
1 H.C. 37	Buerger's disease, infected B.K. stump	—	+	Revision. Excision extensive draining sinus. Closure	5	+
2 W.J. 45	Pseudo-Buerger's disease, recurrent stump infections	Staph. aureus	+	Wide excision of infected area. Closure	12	Healed primarily. Later recurrence of sinus due to F.B.
3 C.J. 50	Abscess of stump	Staph. aureus	+	Revision, closure	8	+

TABLE VI.—CONTAMINATED CHOLECYSTECTOMY WOUNDS, CLOSURE

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Antibiotic*	*Treatment*	*SK-SD, days*	*Healing*
1 O.T. 68	Acute cholecystitis pyogenic gallbladder pyoperitoneum	No growth	+	Cholecystectomy, closure, stab drainage	7	+
2 G.B. 75	Subsiding acute cholecystitis	E. coli	+	Cholecystectomy, appendectomy, closure, stab drainage	7	+

INFECTED AMPUTATION STUMPS

Three patients have been treated with SK-SD instillation following revision of amputation stumps in the presence of gross infection. Rather striking results were obtained in Patient 1 (Table V) who had severe Buerger's disease and infection of long standing in his stump. The old inflamed and indurated incision was open at its midportion for a distance of 3 centimeters, and active purulent drainage emitted through this defect from a sinus which extended in toward the femur, a distance of 5 to 6 centimeters. The stump was revised and the grossly contaminated flaps closed. Small Penrose drains and polyethylene catheters were inserted at each end of the closure for SK-SD instillation and drainage. Rapid primary healing ensued. Similar results were obtained in Patient 3, following revision of the stump and removal of grossly infected tissue. In Patient 2, however, a sinus tract developed in the incision several weeks after healing had occurred, and it was necessary to reopen the stump and explore the depths of the sinus for a foreign body. None was found and the defect was left open, since use of the enzymes will usually not aid healing if a foreign body is still present in a wound. Thus, in these patients, definitive results were obtained in 2 out of 3, results which were unexpected considering the degree of gross contamination and relatively poor blood supply of the tissues involved. Data on these patients are presented in Table V.

CHOLECYSTECTOMY INCISIONS

Only 2 cholecystectomy incisions have been treated by SK-SD instillation. The incidence of abdominal wound infection following biliary tract surgery is probably somewhat more frequent than commonly supposed. A review of elective cholecystectomy, emergency cholecystectomy, and elective choledochotomy in this hospital from 1948 to 1952 indicates the following: Infection developed in 4 (9.9 per cent) of 44 cases of emergency cholecystectomy, in 10 (6.1 per cent) of 164 cases of elective cholecystectomy, and in 5 (6.8 per cent) of 73 cases of elective choledochotomy.

In these cases, the method used for instillation of SK-SD was the same as in the appendectomy incisions. Tube and drain were inserted into the subcutaneous fat from the lateral end of the closed incision. The patient was then positioned obliquely so that the drainage hole was uppermost, and was kept in this position for from 4 to 6 hours after which he was turned on his right side for drainage. Because of the excess adipose tissue commonly encountered in

TABLE VII.—SECONDARY CLOSURE OF INFECTED INCISIONS

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Antibiotic*	*Treatment*	*SK-SD, days*	*Healing*
1 A.L. 40	Postappendectomy wound infection, ruptured. Diabetes	E. coli, hem. strep.	+	Secondary closure	6	+
2 T.G. 55	Postappendectomy wound infection, periappendicitis	Hem. strep.	+	Secondary closure	11	+
3 J.S. 67	Abdominal wound infection. Separation. Procotosigmoidectomy for ca. of rectum	Proteus hem. staph. aureus, enterococci	Bowel prep. +	Secondary closure. Revision of colostomy	22	Unsuccessful. Reseparation of wound
4 H.T. 67	Abdominal wound infection and separation. Intestinal obstruction	Pseudomonas aerog.	+	Secondary closure	7	Unsuccessful. Reseparation of wound
5 N.W. 31	Inguinal hernia, incisional abscess	Hem. staph. aureus	+	I & D of abscess. Secondary closure	11	+
6 E.Z. 41	Abdominal wound hematoma, infection separation. Proctosigmoidectomy for ca. of rectum	Hem. staph. aureus	+	Secondary closure	9	Slow progressive healing

patients with biliary tract disease, use of SK-SD would appear to be a useful adjunct in assuring wound healing when contamination of the incision has occurred from removal of an acute gangrenous gallbladder or from spilled and possibly infected bile.

SECONDARY CLOSURES OF INFECTED INCISIONS

As with appendectomy incisions, closures in this group provide a good test of the method being used. Closure and enzyme instillation have been performed on 6 patients, the data on which are presented in Table VII. Of these, 4 incisions were successfully healed while 2 were not. Following lower abdominal operations, Patients 3 and 4 both had infected incisions which had undergone separation. Closure with retention sutures was done with considerable tension exerted on the wound edges. Although the infection in each was débrided considerably by the enzymes instilled, both wounds separated, one partially, upon removal of the sutures. It is believed that healing would have occurred uneventfully were it possible to close the wounds without undue tension.

DEEP ABSCESSES

Although this category varies from the other in which contaminated incisions are closed, its inclusion in this paper is thought to be warranted because evidence is noted that incisions for drainage need not be as extensive if SK-SD instillation is used. Or if large incisions are made for the evacuation of an abscess, they may be largely reclosed, leaving only an aperture sufficient to allow free drainage of products of enzymatic lysis.

Streptokinase and streptodornase were well tolerated in the deep abscesses into which they were instilled (Table VIII). Free drainage must be afforded following the 6 hour period of contact and for this reason drainage through a catheter alone cannot be relied upon. Inadequate drainage occurred in Patient 9 who had a deep left subphrenic abscess. A No. 24 F. catheter was first threaded into this abscess through a small opening in the abdominal wall. Drainage was poor, and resolution of the abscess was delayed until the incision was enlarged and Chaffin-Pratt suction instituted. This type airvent suction has been found to be more effective than large cigarette drains. Our favorable results with the instillation of enzymes into abscesses seems to support the observations of Collins and co-workers who found a reduction in morbidity, hospital stay, and duration of drainage in a series of patients with pelvic cul-de-sac and tuboovarian abscesses treated with SK-SD.

TABLE VIII.—USE OF SK-SD IN TREATMENT OF DEEP ABSCESSES

Case No. Patient Age, yrs.	*Lesion*	*Culture*	*Antibiotic*	*Treatment*	*SK-SD, days*	*Healing*
1 S.H. 50	Retroperitoneal abscess	Hem. staph. albus	+	Air-vent suction	7	+
2 R.C.T. 28	Pelvoperitoneal abscess postappendectomy	E. coli	+	SK-SD started on 11th p.o. day through drain	7	+
3 E.D. 38	RUQ abdominal wall abscess after gastric resection	Pseudomonas aerog.	+	I & D. 2 cm. incision 2 catheters inserted	10	+
4 J.G. 23	Pericecal abscess p.o. appendectomy	Proteus hem. strep. Strep.	+	I & D. 4 cigarette drains and catheter	13	+
5 R.G. 30	Liver abscess, probably amebic	0	+	I & D. Polyethylene tube	12	+
6 E.B. 27	Pericecal abscess p.o. appendectomy	E. coli, hem. strep.	+	I & D. Penrose drains. Polyethylene tube	6	+
7 W.Z. 29	Large pelvic abscess RO. Rupt. appendix	E. coli, entero-cocci	+	I & D. Drains, catheter	8	+
8 T.W. 41	Large anterior perineal abscess	Nonhem. strep. hem., staph. albus	+	I & D. Polyethylene	7	+
9 R.M. 25	Left subphrenic abscess p.o. partial colectomy. Ulcerative colitis	E. coli, Strep. faecalis	+	I & D. catheter Air-vent suction	13	Satisfactory resolution after air-vent suction used
10 J.R. 58	Hepatic abscess	B.-Strep.	+	I & D. catheter	25	+
11 S.R. 33	Episacral abscess from caudal anesthesia	Proteus gram + cocci	+	I & D. catheter	12	+
12 T.S. 26	Episacral abscess from caudal anesthesia	Hem. staph. aureus	+	I & D. catheter	10	+

REACTIONS TO SK-SD

Fever. No significant febrile reactions comparable to those which occasionally occur following instillation of SK-SD into the thoracic cavity have been noted in the groups of patients presented here. It is of interest, however, that in a separate study of the effects of SK-SD instillation on primary healing we have noted that significant spiking temperatures have not been uncommon following instillation of the enzymes into the interstices of closed pilonidal incisions. Why this febrile rise occurs in these incisions, and does not occur following instillation into those incisions on the abdomen or extremities, is obscure.

Bleeding. Among those patients whose posterior defects were closed following abdominal perineal resection (Table IV), SK-SD instillation was discontinued in Patients 1 and 5. In Patient 1 passage of old blood occurred from the wound 3 days after the enzymes were started. No fresh bleeding was observed, and it was thought likely that enzymatic action had possibly lysed a large clot resulting from immediate postoperative bleeding. Patient 5 displayed a bleeding diathesis of unknown type; fresh bleeding from the perineal wound led to a rather marked anemia requiring transfusions. Laboratory determinations showed no abnormalities in clotting, bleeding, or prothrombin values. During the transfusing of the patient for this anemia, however, a decided transfusion reaction occurred. It is possible, therefore, that the bleeding may have been caused by mismatched blood given at the time of operation. In the course of enzymatic

débridement of surface lesions with SK-SD, 3 patients, not included in these series bled profusely. In 1 of these, vigorous bleeding occurred twice from the transverse cervical artery following radical neck dissection and required re-ligation. In this case insecure ligation would appear to be a more likely cause of bleeding than enzymatic action. In 2 other similar patients bleeding also occurred. In 1 patient SK-SD were instilled into a dental abscess which had been opened and drained; in the other, bleeding ensued from the scarred wound following excision of a recurrent thyroglossal duct cyst. In these 2 instances, it is postulated that hemostasis was insecure at the time of surgery, and that enzymatic lysis of clots on the blood vessels resulted in the renewal of the bleeding.

Cellulitis. Cellulitis will result if SK-SD are injected into normal tissues from which they cannot drain, or if allowed to dissect into planes of normal tissue from a wound in which they are being used. For this reason, careful attention to adequate drainage must be observed. Early in the use of SK-SD in closed incisions a few instances were noted in which cellulitis occurred in the normal tissues dependent to the incision. This result was found to be due to inadequate drainage of the enzymes around the tube through which they were introduced.

Allergic manifestation. No allergic reactions have been recognized. Almost all of the patients treated have received only one course of SK-SD instillation, hence, manifestations indicating the development of sensitivity could not be determined.

DISCUSSION

It would appear that the use of SK-SD instillation following closure of contaminated incisions favorably influenced the uncomplicated healing of most of the patients described in the foregoing. No one can be dogmatic in claiming results in studies involving wound healing where many uncontrolled factors are involved. In a discussion of this problem, Bower points out that wound healing varies with the race and individual, and even in the same individual according to the body area involved. Variations are found in the invading organisms, the vitamins, electrolytes, nutritional and fluid balance of the tissues of the host, and local blood supply and mobility of the part treated. In this study, the resistance of the patient to the infection present and the sensitivity of the organisms to the antibiotics used are important but largely unmeasured factors. Age of the patient and the presence of concomitant disease, such as diabetes, are likewise important influences on wound healing. The difficulty of evaluating results, such as those obtained in this study, is augmented by the known fact that contaminated incisions will occasionally heal if they are closed, drainage is afforded, and the patient is placed on antibiotic therapy. There is insufficient assurance, however, that uncomplicated healing will always take place especially in grossly contaminated incisions. For this reason, the surgeon is more likely to elect a more conservative procedure, such as leaving the skin and subcutaneous tissue open following operation for a ruptured appendix and subsequently compressing and secondarily closing the incision.

If proteolytic enzyme instillation on extended trial should prove to constitute a means whereby immediate closure could be performed with assurance of subsequent healing, then our methods of achieving wound healing with lessened morbidity and hospitalization for the patient are augmented. As stated before, wound infection occurred in 39 of the 81 patients with ruptured appendices treated by current methods in the past 6½ years in this hospital. In the small series of 18 patients with ruptured appendices treated with SK-SD instillation into primarily closed incisions, satisfactory healing was obtained in 16 and superficial suppuration in only 1 of 2 additional patients. As these cases were selected for trial of enzyme instillation because of the presence of unmistakable gross soilage of the

incisions, it is believed that a larger number of significant wound infections would have resulted if treatment by current methods had been carried out.

For the purpose of standardization of technique and reduction of variables, no antibiotic drugs were used with the enzyme solution in this study. It is likely that when antibiotic sensitivities of the contaminating bacteria can be determined, addition of the proper antibiotic agent would be of definite topical value and augment the parenteral effects.

The optimal use of any method of favorably influencing wound healing is found when blood supply is compromised by disease such as diabetes, Buerger's or obliterative vascular disease as well as in elderly individuals whose natural powers of resistance are on the wane. Concomitant with the method presented in this report, it is emphasized that the usual points of good surgical technique must be observed, i.e., careful hemostasis, closure without undue tension, attention to attaining contact between enzyme solution and substrate for a period of 4 to 6 hours, and the provision of adequate drainage for the removal of the products of enzymatic lysis.

The question arises as to whether an important factor in the achievement of the results in this study is due to the promotion of improved drainage by the enzymes rather than by the lytic action they exert. This may very well be true, especially when the enzymes are used prophylactically in contaminated incisions.

SUMMARY

1. A method permitting immediate closure of contaminated incisions utilizing the instillation of streptokinase and streptodornase into the interstices of the closed wounds is described. The method has been used in 73 patients divided among the following categories: ruptured appendices, colon operations, draining sinuses, posterior wounds of abdominoperineal resections, infected amputation stumps, cholecystectomy incisions, secondary closure of infected incisions, and deep abscesses. Results have been uniformly favorable, and it is believed that the method constitutes a useful adjunct to careful operative technique and antibiotic therapy in achieving successful immediate closure of wounds which would usually be left open or secondarily closed.

2. Since the liquefying and irritating properties of SK-SD aid in promoting drainage from the closed wounds, improved drainage is possibly an important factor in achieving the results obtained in this study.

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PITUITARY ADENOMAS, CARCINOMAS, AND CRANIOPHARYNGIOMAS

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THE PRESENT ARTICLE constitutes a report of 172 cases of intrinsic pituitary tumors and craniopharyngiomas seen at the University of California and Franklin Hospitals (the majority at the former) from 1913 to 1951. The series consisted of 100 cases of chromophobe adenoma (77 verified by surgery, 12 presumptive diagnoses, and 11 asymptomatic at autopsy), 33 of acromegaly, 23 of craniopharyngioma, 4 of malignant adenoma, 4 of basophil adenoma, and 8 of metastases to the pituitary. The group does not reflect a uniform method of therapy, for the patients have been treated by different members of the attending[1] and resident staffs of the two hospitals over this 38 year period, during which many refinements have taken place in the diagnosis and treatment of these lesions. This fact in itself, we believe, lends value to the series.

CHROMOPHOBE ADENOMAS

There were 77 cases of verified chromophobe adenoma. Of this group 43 were males and 34 females.

The ages of the patients at the time of admission to the hospital or first visit to the clinic varied from 17 to 72 years, the average being 42 years. Sixty-four patients (83.1 per cent) were between 30 and 60 years of age. The youngest patient, aged 17, had had symptoms since the age of 12. The age distribution is shown in Figure 1 and in Table I.

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The duration of symptoms of 76 patients ranged from 3 months to 18 years, the average being 3.7 years. Actually, in many cases, the symptoms may have been of longer duration than that recorded in the histories, since the initial symptoms were often slight and their exact onset difficult to fix in retrospect.

The incidence of the various symptoms consisted of: visual impairment in 74 cases, headache in 53, endocrine symptoms in 38, diplopia in 19, extrasellar extension in 8, and rhinorrhea in 2. By far the most frequently encountered symptom was visual impairment, which was reported by all except 2 patients. One of these patients was in an impaired state of consciousness on admission, and visual field changes were subsequently found on examination. The changes were often slight, and might have passed unnoticed had they not been accompanied by other symptoms.

The incidence of diplopia was high (25 per cent) despite the fact that only 3 patients had objective evidence of ocular muscle palsy; this has been noted previously and several plausible explanations proposed. Kubie and Beckmann suggested that when macular vision is impaired, the patient diverges his eyes and employs both nasal fields for central vision, diplopia thus resulting from the use of heteronymous fields. Bardram mentions the possibility of slight ocular muscle paresis without overt impaired ocular mobility, or defective fixation secondary to impaired central vision causing a disturbance of binocular vision. He favors the latter explanation.

Endocrine symptoms included amenorrhea, weight changes, diminution or loss of libido, changes in water balance, and hypersensitivity to environmental temperatures. Among the symptoms of extrasellar extension were olfactory hallucinations, facial numbness, and diplopia. The latter, however, may result from other causes as already pointed out.

Of the objective findings, changes in the visual fields were most common, having been found in all 77 patients (Table II). Fifty-two (67.5 per cent) had complete or partial bitemporal hemianopia. In 12 patients, one eye was blind or reduced to bare light perception, and the other eye was affected. These may have been advanced cases of bitemporal hemianopia. In 7 patients, only one eye was affected, 4 having temporal hemianopia, 1 nasal hemianopia, and 2 bare light perception in the affected eye. Two patients had complete blindness of one eye and only light perception in the other, so that no determination of the visual field was possible. Two patients had homonymous hemianopia, 1 showed generalized constriction of the visual fields, and 1 had slightly enlarged blind spots in the absence of apparent papilledema.

Some of the other findings which are listed in Table II merit further comment. One patient had calcification within an enlarged sella turcica; 1 of the 2 patients with a normal sella showed suprasellar calcification. (Lindgren and Di Chiro reported calcification in 3 per cent of their series of 345 pituitary adenomas.) The lowest basal metabolic rate recorded was −32.8 per cent. Three patients had an elevated basal metabolic rate, the highest being +17 per cent. This latter patient, a 38 year old male, had had a thyroidectomy 9 months previously, at which time he had mild exophthalmos and basal metabolic rate was +47 per cent. He showed no other signs pituitary dysfunction.

Blood pressure was elevated mainly in the older age group. Hypertension has not appeared to be related in any way to chromophobe adenoma.

Seventy-five patients were operated upon a total of 92 times (excluding encephalography, arteriography, and 5 reoperations for postoperative clot, surgical complications, or removal of an infected bone flap). There were 15 postoperative fatalities, giving an operative mortality of 16.3 per cent, and a case mortality of 20 per cent. Eleven of the deaths occurred prior to 1940. The operative mortality for 74 primary operations (1 patient having had a previous subtemporal decompression and x-ray therapy elsewhere) was 13.5 per cent and for the 18 reoperations 27.8 per cent. Eighty-four frontotemporal craniotomies were performed with a mortality of 15.4 per cent, and the mortality of 8 transphenoidal operations was 25 per cent.

Nine of the 15 deaths occurred in patients with extrasellar extensions of the tumor. One of these had marked hyperthermia; severe hemorrhage from the tumor occurred in another. Jefferson reported a mortality of 33 per cent in patients with extrasellar extensions, compared with 2 per cent in cases without them. Horrax stated the operative risk to be 30 to 40 per cent with extrasellar extensions as opposed to 3 to 5 per cent without them.

There were 2 deaths from intracranial infection, 1 death from meningitis following a transphenoidal operation, and 1 from a wound infection and brain abscess. One patient died of pneumonia and pleural effusion, 1 of an intracerebral hemorrhage, and 1 of a postoperative subdural hematoma. One patient had a glioma of the frontal lobe in addition to the pituitary adenoma and has been reported in detail elsewhere (15).

The early results of treatment in 65 patients alive after primary operation were as follows:

Vision was improved in 71 per cent, unchanged in 17 per cent, and worse (immediately or subsequently) in 12 per cent.

Twenty-one patients (32 per cent) remained well 1 to 19 years postoperatively. Two additional patients (3 per cent) died of incidental causes after remaining well for 4

and 14 years respectively. Eighteen cases were either too recent for evaluation or lost to follow-up. Recurrence developed in 22 cases (34 per cent). Of these patients, 6 died after further treatment, 2 died elsewhere without treatment, 5 are untraced after further treatment, 7 are well 1 month to 11 years after further treatment, 1 died elsewhere of unknown cause 5 years after operation for recurrence, and 1 was well 1 year after operation for a second recurrence. Two patients were reported to have died elsewhere of progression of the tumor.

Twenty-four of the 65 patients were treated by operation alone. Of these, 29 per cent are well 1 to 19 years (average 5 years) postoperatively, and 50 per cent had recurrence in 6 months to 7 years (average 3.7 years). There was no follow-up in 17 per cent, and death from an unrelated cause occurred in 4 per cent.

Of the 41 patients who received preoperative or postoperative radiation therapy, or both, 37 per cent are well 1 to 16 years (average 5.8 years) later, while recurrence in 1 to 7 years (average 4 years) took place in 22 per cent. Thirty-four per cent were lost to follow-up or were operated upon too recently for evaluation of late results. The remaining 7 per cent died of recurrence.

There were 12 additional patients with a presumptive diagnosis of chromophobe adenoma. The age incidence, symptoms, and objective findings were similar to those of the patients with verified chromophobe adenoma. Five of this group were treated solely by radiation with subsequent improvement that persisted for periods of from 4 months to 5 years, after which they were lost to follow-up. Five others received no specific treatment or refused treatment, and the operative specimens of 2 were not properly classified and are no longer available.

That chromophobe adenomas may occasionally grow very slowly is demonstrated in 2 patients who received no specific treatment. The first of these, a 56 year old man who had had symptoms for 12 years, was blind and had paralysis of the left oculomotor and trochlear nerves. He refused treatment following examination. According to a letter received from him 3½ years later, however, he was subjectively unchanged. The other patient, a negro female aged 46, whose duration of symptoms was indeterminate, had almost complete bitemporal hemianopia, obesity, amenorrhea, and an enlarged sella turcica. She was followed in the clinic for 7 years, during which time the only change was the development of diabetes mellitus.

TABLE I.—AGE DISTRIBUTION

Age group	*Chromophobe adenoma*[1]	*Acromegaly*	*Craniopharyngioma*
0– 9			5
10–19	3		5
20–29	6	6	5
30–39	24	10	5
40–49 (83.1 per cent)	24	9	
50–59	16	6	1
60–69	3	2	2
70–79	1		
Total cases	77	33	23

[1]Verified at surgery.

In addition to the 89 patients mentioned, there were 11 cases of asymptomatic chromophobe adenomas found incidentally at autopsy. Five patients were males and 6 females. The ages varied from 12 to 63 years, but 9 were in the 40 to 60 age group. The adenomas were discovered on microscopic examination, since the pituitary appeared grossly normal or but slightly enlarged in these cases. Several small adenomas were present in 1 case. So far as can be determined from the records, there were no signs or symptoms of the pituitary tumor.

The causes of death in this group included congestive heart failure, metastatic carcinoma, chronic nephritis, leukemia, retroperitoneal sarcoma, and coronary occlusion. One patient died following exploration of a cerebellar hemangioblastoma which had caused clinical symptoms. At autopsy a microscopic pituitary chromophobe adenoma was present in addition to the cerebellar tumor.

Costello reported finding subclinical adenomas of the pituitary in 22.5 per cent of a series of 1,000 autopsies of patients who had

TABLE II.—OBJECTIVE FINDINGS IN 77 CASES OF CHROMOPHOBE ADENOMA

Findings	*No. cases*
Visual field changes	77
Optic atrophy	62
unilateral.... 16	
bilateral..... 46	
Roentgenograms (recorded in 62 cases),	
enlarged sella	60
normal sella	2
Basal metabolism (recorded in 40 cases),	
low (below minus 10 per cent)	25
	(avg. minus 20 per cent)
high (above plus 10 per cent)	3
	(avg. plus 15 per cent)
Blood pressure,	
systolic 140 or higher	20
systolic 100 or lower	3
Obesity	9
Soft,* delicate skin ("pasty" or yellowish)	5
Trigeminal nerve involvement	3
"Fugitive acromegaly"	2
Decreased body hair	2
Hypertrichosis	2
Oculomotor nerve palsy	2
Facetiousness; impaired ocular convergence; slight facial weakness; bilateral papilledema (extrasellar extension of tumor); hyperglycemia	1 each

*This is a common finding in patients with chromophobe adenomas. These 5 cases represent marked examples of the condition.

no history or findings to suggest pituitary dysfunction during life. Of these adenomas, 52.8 per cent were chromophobe, 7.5 per cent chromophil, 27.2 per cent basophil, and 12.4 per cent mixed.

EOSINOPHILIC ADENOMA

There were 33 cases of acromegaly in the series. Since the clinical picture of acromegaly is practically unmistakable, we have included those patients not operated upon with those whose tumors were proved by biopsy or postmortem study. There were 13 males and 20 females with this condition. The average age was 41 years. The age distribution is shown in Figure 1 and in Table I.

TABLE III.—SYMPTOMS OF ACROMEGALY IN 32 CASES

Symptoms	*No. cases*
Abnormal growth (features, etc.)	32
Headache	26
Impaired vision	17
Lethargy, fatigue	17
Weight gain	15
Amenorrhea (20 females)	12
Diplopia	7
Loss of libido (12 males)	5
Loss of libido (20 females)	1
Weight loss	1

Symptoms unknown in 1 patient—see text.

The symptoms were known in only 32 cases, 1 patient having died shortly after admission in coma. The duration of symptoms varied from 6 months to 30 years, with an average of 6.8 years. The symptoms and their incidence are given in Table III.

Table IV lists the objective findings in the 33 cases. The roentgenograms or reports thereof were available in 25 cases, and all showed 1 or more of the usual changes associated with acromegaly (i.e., enlarged sella, prognathism, thickened calvarium, tufting of terminal phalanges). Eighteen patients (54.5 per cent) had visual field changes. Eleven patients had bitemporal hemianopia, but in 6 of these it was partial or involved the superior quadrants only. Three patients had temporal hemianopia of one eye with blindness or light perception only in the other eye. Unilateral temporal hemianopia was observed in 1 patient. Homonymous hemianopia was observed twice and slight generalized constriction of the fields once.

The abnormalities of glucose metabolism were generally not severe, usually being evident only on the glucose tolerance test. One patient, however, had severe diabetes for several years and died in diabetic acidosis and 1 other patient required insulin. Nine patients had systolic blood pressures of 140 or higher. The highest pressure, 240/140, was recorded in a 47 year old female, in whom hypertension was discovered 8 years before the onset of symptoms of acromegaly. The next highest pressure, 190/145, occurred in a 37 year old female with chronic nephritis. In the others, the pressure elevation was slight—the lowest being 102/75.

Records of the basal metabolic rate were available in 17 cases. In 6 patients, the rate varied from +12 to +16 per cent. One patient had a basal metabolic rate of −13 per cent, determined about 6 months after the onset of acromegaly. Eleven years later, during a period of mild cardiac decompensation, his basal metabolic rate was +30 per cent.

Therapeutically, these patients fall into three groups. The first consists of 7 patients who received no specific therapy (i.e., neither surgery nor radiation), either because the condition appeared to be static ("burned out") or because treatment was refused. No follow-up was available for 4 patients of this group. Two were essentially unchanged, except for an improved glucose tolerance in 1 patient, 1 year after the first visit, with no further follow-up. One patient died in diabetic acidosis 9 years after the onset of acromegaly.

In the second group, 14 patients were treated exclusively by radiation, each receiving 1 or more courses of x-ray therapy to the pituitary with or without supplementary hormonal therapy. In 11 of these patients, the condition was arrested or improved for from 1 to 25 years (10 years or over in 5 cases). Generally, there was little if any regression of the changes in features and bones. Glucose tolerance improved in 3 patients, and 1 of these patients with overt diabetes mellitus was able to discontinue the use of insulin. One of these cases was reported by Allen and Lisser. Following treatment, headache subsided in 3 patients, and visual fields improved in 2 patients.

Two patients survived 14 and 16 years after x-ray therapy, dying of unrelated causes. In 1 patient the acromegaly was arrested, in the other slowly progressive.

One patient died while receiving x-ray therapy. At autopsy, a cystic eosinophilic adenoma was found extending out of the sella and compressing the hypothalamus.

The third group includes 11 patients treated surgically. Fifteen operations were performed with 1 death, an operative mortality of 6.6 per cent and a case mortality of 9 per cent. There were 8 frontotemporal craniotomies with 1 death, and 6 transphenoidal operations with no deaths. One subtemporal decompression was performed in 1924. (A second patient had had a subtemporal decompression in 1932 prior to coming to this clinic.) Most patients had x-ray therapy before or after operation, or both.

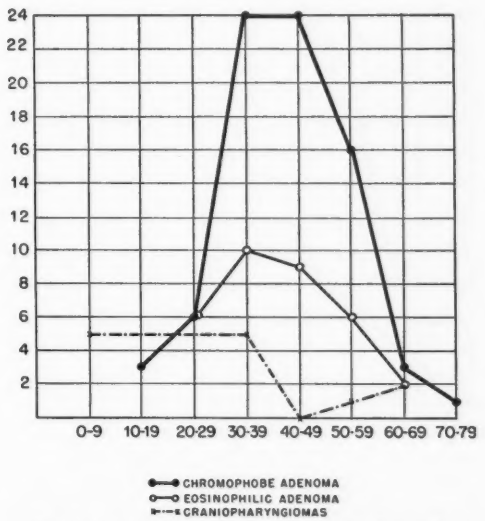

FIG. 1. Age incidence in patients with pituitary adenomas and craniopharyngiomas.

The immediate postoperative results in regard to vision were generally good (studied as soon after operation as careful perimetry could be done). One patient died 1 month postoperatively of an incidental cause. There were recurrences in 2 patients, 1 and 6 years postoperatively, which responded to x-ray therapy. Five cases were improved or arrested for from 1 to 18 years. There were insufficient follow-up data in 2 cases, and 1 patient, though doing well, was operated upon too recently for evaluation.

In recent years the general policy has been a trial of x-ray therapy in patients with acromegaly who have no visual field chang-

TABLE IV.—OBJECTIVE FINDINGS IN 33 CASES OF ACROMEGALY

Findings	*No. cases*
Physical signs of acromegaly	33
Roentgenographic changes (reported in 25)	25
Visual field changes	18
Abnormal glucose tolerance or overt glycosuria	14
Elevated blood pressure	9
Enlarged thyroid or previous thyroid surgery	6
Ocular muscle weakness	1
Trigeminal hypalgesia (1 and 2 divisions)	1
Basal metabolism (recorded in 17)	
elevated (above +10 per cent)	6 (avg. +14 per cent)
depressed (below −10 per cent)	1 (avg. −13 per cent)

es. Operation is resorted to mainly for progressive visual disturbances unaffected by radiation. Three patients were operated upon in 1951 because of intolerable headaches subsequent to or unaffected by x-ray therapy. One patient noted improvement, but 2 are still not free of the complaint of pain.

CRANIOPHARYNGIOMAS (TUMORS OF RATHKE'S POUCH)

There were 23 verified cases of craniopharyngioma[2] in this group. Sixteen patients were males and 7 females. The youngest patient was 4 years of age and the oldest 69, the average for the group being 25.9 years. Only 10 patients (43 per cent) were under 20 years of age, an interesting finding in view of the fact that some have considered this primarily a tumor of childhood and adolescence. However, there seems to be a decreased incidence after the age of 40 (Fig. 1). The age distribution of the group is shown in Figure 1 and Table I.

The symptoms were known in all cases. The duration of symptoms prior to hospitalization varied from 7 months to 7 years, the average being 2.5 years. Table V lists the symptoms and the frequency of each. The number of children in the group affects the incidence of various symptoms when compared with the other tumors.

One patient, a 24 year old female, was of unusual interest in that, during the several months prior to entry to the University of California Hospital (and 6 years after the onset of symptoms of the tumor), she developed recurrent episodes of Hemophilus influenzae meningitis, though there was no evidence of a cerebrospinal fluid leak. At intracranial operation, pus was aspirated from an intrasellar and suprasellar mass which was subsequently drained through a sphenoidotomy. Biopsy of the abscess wall showed the lesion to be a craniopharyngioma.

[2]Controversy exists regarding the correct name of these tumors. Craniopharyngioma is the term used in *Standard Nomenclature of Diseases and Operations*. 4th ed. Philadelphia: The Blakiston Co., 1952.

Changes in the visual fields were the most common objective finding. Twelve patients had bitemporal defects, either partial or complete and usually incongruous; 2 had homonymous hemianopia. Two patients had temporal defects in one eye with bare light perception or complete blindness in the other eye. There was 1 example of each of the following visual field changes: unilateral temporal defect, unilateral blindness, and bilateral blindness. The visual fields were normal in 1 case, and unknown or not tested in 3 (children).

Bilateral optic atrophy was present in 10 patients, papilledema or blurred disc margins in 7, and unilateral optic atrophy in 2. There was no record of the ophthalmoscopic findings in 4 patients.

Skull roentgenograms or reports thereof were available in 15 cases. The sella turcica was enlarged or eroded without calcification in 6 cases. A normal sella with suprasellar calcification was reported in 4 cases, and an enlarged or eroded sella with intrasellar or suprasellar calcification in 3. Completely normal studies were reported twice (13 per cent). Thus, intracranial calcification was noted in 7 cases (47 per cent), and abnormality of the sella in 9 (60 per cent), a lower incidence than that reported by McKenzie and Sosman (71 per cent and 76 per cent respectively) but close to the figures of Love and Marshall (56 per cent and 63 per cent).

The clinical picture of hypopituitarism was present in 4 cases, 1 of these patients having severe pituitary cachexia. In addition, there was 1 instance of dwarfism, and 1 of Fröhlich's syndrome. Basal metabolism rates, recorded in 4 cases, were −34 per cent, −32 per cent, −24 per cent, and −18 per cent. Involvement of the abducens nerve was noted in 4 patients, trigeminal nerve in 3, facial nerve in 2, and oculomotor in 1 patient. Hemiparesis was present in 3 cases, and confusion or stupor in 2. A "cracked pot" sound was elicited in 2 children. Nystagmus and diabetes insipidus were present in 1 case each. One patient, a 4 year old boy,

presented the clinical picture of meningitis, with over 2,000 leucocytes in the spinal fluid, but no organism was obtained on smear or culture. At operation, an intrasellar craniopharyngioma was partially removed.

Thirty-seven operations were performed on these 23 patients with 8 deaths, an operative mortality of 21.6 per cent and a case mortality of 34.6 per cent. One death followed a ventriculogram and another followed subtemporal decompression. The mortality of the primary operations was 21.7 per cent, including the death after ventriculography.

Of the 18 patients who survived the initial operation, 14 were improved during the early postoperative period. One of the patients noted decreased headache and relief of diplopia for 5 months after a negative posterior fossa exploration. Two patients were unchanged, and 2 became progressively worse.

The late results among these 18 patients were not encouraging. One patient died 6 months postoperatively, presumably of recurrence, 2 were untraced, and 3 were well 5, 2½, and 1 year after operation. Recurrence or continued tumor growth occurred in the remaining 12 patients. Three of these died, or were getting worse at last report. One received radiation therapy and has remained unchanged for 11 years (16 years after the original operation).[3]

Eight patients had 1 or 2 reoperations, with 3 postoperative deaths. Two patients died subsequently, 2 were well 1 year postoperatively, and 1 patient was operated upon too recently for evaluation.

The question of the effect of radiation therapy on craniopharyngiomas is unsettled, although several authors have noted beneficial effects in occasional cases, Leddy and Marshall suggesting that roentgen therapy inhibits formation of fluid within the cyst. One of our patients received preoperative x-ray therapy, with visual improvement and relief of headache for 5 months. Five patients received postoperative radiation, with no effect in 2 cases. Two patients remained improved for 1 year, with no further follow-up. In the fifth case, the tumor was visualized but could not be removed. Radiation therapy was given, and visual impairment and other symptoms, except those of hypopituitarism, were improved for 7 years. Because of recurrence, radiation therapy was again instituted, with improvement for 2½ years, followed by death.

Two other patients received x-ray therapy for recurrence following operation. There was no effect in 1 patient. The other patient, mentioned previously, is the only one in this series known to be alive more than 10 years postoperatively. He received x-ray therapy for a recurrence 5 years after operation and has remained well, except for hypopituitarism, for 11 years since.

TABLE V.—SYMPTOMS OF CRANIOPHARYNGIOMA IN 23 CASES

Symptoms	*No. cases*
Visual impairment	21
Headache	19
Lethargy, fatigue	13
Diplopia	7
Vomiting	6
Weight gain	6
Weight loss	4
Amenorrhea	3
Polyuria	3
Personality change	2
Failure to grow (child)	2
Ataxia	1
Convulsions	1
Loss of libido	1
Meningitis	1

CARCINOMA OF THE PITUITARY (MALIGNANT ADENOMA)

The criteria and terminology of this group of tumors have been disputed. Henderson called them all adenocarcinomas, although only 1 case in 11 showed distant metastases. His criteria included frequent mitoses, variation in cell size and shape, and invasion, especially of dura and bone. Jefferson, on the other hand, differentiated between malignant adenoma and carcinoma, on the

[3]Since this article was prepared, this patient re-entered the hospital because of progressive right hemiparesis present for 1½ years. Craniotomy revealed no evidence of tumor, but there was arachnoiditis about the optic chiasm and nerves, and brain atrophy (? x-ray effect).

basis that carcinomas metastasized. A malignant adenoma was defined as one that had broken through its capsule, often showing extensions into the cavernous sinus, and that microscopically showed mitoses with loss of cellular pattern and grouping, although Jefferson pointed out that ordinary hypophyseal adenomas may have these same cellular changes. Kraus classified as carcinoma those pituitary tumors that show infiltrative growth and anaplasia of tumor cells, although metastases are seldom observed. King, in reporting a case of carcinoma of the pituitary without metastases, followed the criteria of Kraus. Bailey and Cutler reported 3 cases which they called malignant adenomas, since the tumors manifested most of the criteria used to establish malignancy in tumors of other organs, but not metastases.

The disagreement over terminology appears to be mainly semantic. Certainly, metastasis is not essential to the diagnosis of carcinoma in other regions of the body. Consequently, we believe that, regardless of metastases, those tumors should be classified as carcinoma which show macroscopic or microscopic evidence of invasion of connective tissue, nerves, or bone by the tumor. Anaplasia of the tumor cells is not sufficient to establish carcinoma, since, as pointed out by Jefferson, mitoses, irregularity in cell grouping, and lack of pattern may be found in chromophobe adenoma.

There were 4 cases in our series that fulfilled these criteria. All were males, and their ages were 26, 52, 55, and 58 years. Duration of symptoms varied from 4 to 10 years. Three patients had symptoms of extrasellar extension, namely, facial pain, uncinate seizures, and mental confusion and disorientation, in addition to the usual symptoms associated with an intrasellar neoplasm.

Five frontotemporal craniotomies were performed on these 4 patients with 1 operative death. The 3 survivors all received postoperative radiation therapy. One patient died 3 years postoperatively of progression of the tumor, in spite of having received an estimated x-ray tumor dose of 7,160 roentgens. One patient survived 15 years, dying of an unrelated cause. One patient is still living 3 years after a second operation (the first operation was performed 8 years prior to the second).

Thus, as pointed out by Henderson, there would appear to be two clinical groups of malignant pituitary tumors. In one group, the history, signs, and end results are quite similar to those of benign chromophobe adenoma. In the other group, which often show cranial nerve palsies, there is little or no improvement following surgical or radiation therapy.

BASOPHIL ADENOMAS

There were 4 patients with basophil adenomas of the pituitary. The adenomas were small, did not enlarge the sella turcica, and were found at autopsy in association with adrenal cortical hyperplasia or adenomas in patients with Cushing's syndrome.

Crooke's changes of pituitary basophils and basophilic hyperplasia were found in other instances of Cushing's syndrome, but these lie outside the scope of the present report.

METASTATIC TUMORS TO THE PITUITARY

There were 8 cases in this group. The anterior lobe of the pituitary was involved by metastases in 2 patients with carcinoma of the stomach, 1 with carcinoma of the breast, and another with carcinoma of the thyroid. The posterior lobe contained metastases in 1 patient with carcinoma of the breast. In another patient, the capsule of the pituitary was infiltrated with metastases from a neuroblastoma of the left adrenal. One patient had metastases from a carcinoma of the pancreas in both anterior and posterior lobes of the pituitary. The metastases in these cases were either microscopic or small macroscopic lesions, and no symptoms referable to them were noted during life. They were found at autopsy in association with more or less widespread metastases elsewhere in the body.

In 1 patient with a neuroepithelioma of the maxillary antrum, the tumor was found at autopsy to have invaded the orbit, cribiform plate and ethmoids, and to have infiltrated the pituitary.

Kraus stated that metastatic carcinoma was more common than sarcoma in the pituitary. In his experience, the most frequent primary sites were the breast, lungs, and thyroid. He believed that the posterior lobe was usually involved first, which is at variance with the findings in our small series.

Of course, other lesions in and about the pituitary, such as gliomas of the hypothalamus and optic chiasm, meningiomas of the tuberculum sellae, aneurysms, and chordomas may mimic the pituitary tumors closely. These fall outside the scope of this report, but 1 case will be briefly reviewed as an example.

A 48 year old female had had menstrual irregularities for 9 months, generalized headaches for 6 months, and failing vision with diplopia for 3 months. Examination revealed bitemporal hemianopic field defects, more severe on the right, with a right external rectus paralysis. Roentgenograms demonstrated an enlarged sella turcica with early destruction of the posterior clinoid processes. At craniotomy a yellow-white mass anterior to the optic chiasm was partially removed, and microscopic sections showed chordoma. The patient died on the seventh postoperative day. At autopsy the tumor mass filled the sella turcica and sphenoid sinus, extended down the clivus, and compressed the hypothalamus and pons.

SUMMARY

The symptoms, objective findings, and results of treatment of 172 cases of intrinsic tumors of the pituitary and craniopharyngiomas seen at the University of California and Franklin Hospitals during a 38 year period are reported. There were 77 verified and 12 unverified chromophobe adenomas, 11 asymptomatic chromophobe adenomas found incidentally at autopsy, 33 cases of acromegaly, 23 craniopharyngiomas, 4 carcinomas of the pituitary, 4 basophil adenomas, and 8 cases of metastatic tumors to the pituitary. The results represent the efforts of a number of men during a period of growing knowledge of the diagnosis and treatment of these lesions.

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NEW PHYSIOLOGIC CONCEPTS RELATED TO THE SURGICAL TREATMENT OF DUODENAL ULCER BY VAGOTOMY AND GASTROENTEROSTOMY

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FAILURES IN THE TREATMENT of duodenal ulcer by vagotomy and gastroenterostomy in this clinic have usually occurred in patients with incomplete division of the vagus nerves or who develop persistent stasis of food in the stomach. Attention has previously been directed to the necessity of dividing all, or nearly all, of the vagus nerves to the stomach in order to abolish the nervous phase of gastric secretion. It is the purpose of the present communication to emphasize the importance of an efficiently functioning drainage procedure whenever the operation of gastric vagotomy is performed. In a previous paper (1) evidence has been presented indicating that duodenal ulcers are usually caused by a hypersecretion of gastric juice of nervous origin and that gastric ulcers are usually due to a hypersecretion of gastric juice of humoral or hormonal origin. The hormonal mechanism of gastric secretion is mediated exclusively by the antrum of the stomach which functions as an endocrine organ, releasing gastrin on contact with certain food substances or when tension develops in the stomach as a result of peristalsis. An excessive secretion of gastric juice of humoral origin may result from prolonged contact of food with the antrum mucosa or as a result of hyperperistalsis, hypermotility, and pyloric stenosis. Hypersecretion of gastric juice with ulcer formation has been produced in dogs by transplanting the gastric antrum into the colon as a diverticulum (3). These findings have focused attention on the possible role of the humoral mechanism of gastric secretion in the etiology of some ulcers in man and to the possibility that they might explain some of the unsatisfactory results seen after vagotomy.

Schmitz, Kanar, Storer, Sauvage, and Harkins and Evans, Zubiran, McCarthy, Ragins, Woodward, and Dragstedt observed that the secretion of gastric juice from vagus denervated Heidenhain pouches in dogs was markedly increased by complete division of the vagus nerves at the level of the lower esophagus. Since the stimulation of gastric secretion in a Heidenhain pouch occurs only in response to a humoral agent, it is apparent that, in some way, division of the vagus nerves markedly stimulates the release of gastrin from the antrum. It is probable that the chief factor producing this effect is stasis of food in the gastric antrum due to a decrease in the tonus and motility of the stomach as a result of the vagotomy. The hypersecretion of gastric juice did not occur in similar animals in which stasis of food in the stomach was prevented by a previous gastroenterostomy placed in the gastric antrum or in animals in which the antrum had been previously resected. A high lying gastroenterostomy failed to abolish this hypersecretion, apparently because it did not provide adequate drainage of the vagotomized stomach.

In 1952 Zubiran, Kark, Montalbetti, Morel, and Dragstedt observed that gastroenterostomy produced a sustained increase

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in gastric secretion in Heidenhain pouch dogs when the stoma was placed in the body or fundus of the stomach, but not when the stoma was placed in the gastric antrum. The stimulation of gastric secretion by a high lying gastroenterostomy did not occur if the gastric antrum had been previously resected, suggesting that the responsible humoral agent is gastrin. A complete and satisfactory explanation for this phenomenon is not yet available. However, bad results from the high lying gastroenterostomy have been frequently observed in the past, and this new observation that such an operation stimulates gastric secretion has caused us to scrutinize the unsatisfactory results that we have seen following vagotomy and gastroenterostomy to determine the reason for these failures.

PATIENTS WITH DUODENAL ULCER TREATED BY VAGOTOMY ALONE

When vagotomy was first introduced in this clinic, it was not combined with a gastric drainage procedure. One hundred and fifty-eight patients with duodenal ulcer were treated by vagotomy alone during the period from 1943 to 1949 with good results in 91 patients (58 per cent), fair results in 18 patients (11 per cent), and poor results in 49 patients (31 per cent). Good results include those patients who are free of symptoms and objective evidence of active ulceration on unrestricted diets and who have returned to work. Fair results are those patients who are free of ulcer symptoms and objective evidence of disease but who still complain of intermittent or persistent gastrointestinal discomfort of some sort. Poor results include postoperative deaths, persistence or recurrence of ulcer symptoms, or incapacity because of gastrointestinal symptoms. An analysis of the poor results following vagotomy alone is presented in Table I.

Twenty-three patients or 15 per cent displayed evidence of persistent gastric retention after the operation. A subsequent gastroenterostomy was performed in 20 of these after which all have remained well.

TABLE I.—ANALYSIS OF POOR RESULTS OF VAGOTOMY FOR DUODENAL ULCER

Result	*No. of cases*	*Per cent*
Proved recurrences	14	8.9
Possible recurrences	4	2.5
Stasis	23	14.5
Gastric ulcer	5	3.0
Erosive gastritis	2	1.4
Postoperative deaths	1	.7
Total	49	31.0

Fourteen patients or 9 per cent had a recurrence of duodenal ulcer following vagotomy alone. Four of these patients displayed a persistent reduction in the fasting nocturnal gastric secretion, while in the remaining 10 the nocturnal secretion returned to the preoperative level. In the 10 whose secretion returned a positive response to insulin hypoglycemia indicated that the vagotomy had been incomplete. Of the 4 patients with a low or normal nocturnal gastric secretion but who developed symptoms of persistent or recurrent ulceration, one is especially instructive. This patient displayed a negative response to insulin hypoglycemia on several occasions (Table II) and probably had a complete vagotomy. This patient had a pyloric ulcer which increased in size following the vagotomy necessitating a subtotal gastric resection 4 months later. X-ray examination taken before the resection indicated marked pyloric obstruction with retention. Although a complete section of the vagus nerves with abolition of the nervous phase of gastric secretion was accomplished in this patient, stimulation of the antral phase was prolonged as a result of obstruction due to the location of the ulcer and to the impaired motility of the stomach as a result of the vagotomy.

Five patients or 3 per cent of the group treated by vagotomy alone subsequently developed a new benign gastric ulcer, and 2 patients developed severe erosive hemorrhagic gastritis which required further surgery. These postvagotomy complications occurred even though the original duodenal ulcer had completely healed and in spite of a persistent reduction in the 12 hour nocturnal gastric secretion to below the normal level.

TABLE II.—RELATION OF RECURRENCE OF ULCER TO NOCTURNAL SECRETION AND INSULIN RESPONSE BEFORE AND AFTER VAGOTOMY ALONE (14 CASES)

12 hr. postop. night secretion in mEq.	*No. of recurrences*	*Positive response to insulin hypoglycemia*	*Negative test*
100 plus	0	0	0
80 to 100	1	1	0
60 to 80	2	2	0
40 to 60	3	3	0
20 to 40	4	4	0
0 to 20	4	3	1
Total	14		

In these 7 patients the time of occurrence of these complications ranged from 2 to 6 years after the vagotomy. A clinical abstract of 1 of these cases is provided.

W. B., No. 21177, was a 63 year old male who underwent a transthoracic vagotomy in January, 1943 for a duodenal ulcer with high grade pyloric stenosis and a crater at the base of the bulb demonstrated by x-ray examination. Preoperative 12 hour nocturnal gastric secretion averaged 1,160 cubic centimeters with a free acidity of 65 clinical units or an output of 75 milliequivalents of free hydrochloric acid in the 12 hour period. Postoperative nocturnal secretion measured 310 cubic centimeters with a free acid of 58 clinical units and a calculated acid output of 18 milliequivalents in the 12 hour period, a reduction of 76 per cent as compared with the control level. The patient remained asymptomatic except for mild symptoms of gastric stasis until 4 years following surgery when he again complained of gnawing epigastric pain occurring after meals and occasionally at night. These symptoms were relieved by food, soda, and vomiting. X-ray examinations at this time revealed a large gastric ulcer on the lesser curvature of the stomach just above the angulus. There was marked deformity of the duodenal bulb and pyloric canal but without evidence of crater. The 12 hour nocturnal gastric secretion measured 620 cubic centimeters with no free acid and the response to insulin hypoglycemia was negative. In April 1947, a subtotal gastric resection was performed and examination of the specimen revealed a large benign gastric ulcer and a healed duodenal ulcer. Following the gastric resection he remained well until his death in 1952 following a leg amputation for diabetic gangrene.

The development of a new benign gastric ulcer following vagotomy alone for the treatment of duodenal ulcer was first observed in this clinic in 1948 and reported in 1949 (2). This interesting complication has also been observed by others and may develop when the vagotomy has been complete and the nervous phase of gastric secretion completely abolished. It has usually been associated with stasis of food in the stomach and it is probable that prolonged contact of the antrum mucosa with food has resulted in a hypersecretion of gastric juice of humoral origin.

Evidence supporting this point of view has been obtained recently in our laboratory by the use of a new test meal, consisting of meat, eggs, milk, toast, and cereal, mixed with barium sulfate. Following the ingestion of this meal, samples of gastric content have been secured at hourly intervals for long periods of time, and the concentration of free hydrochloric acid determined. In several patients in whom a physiologically complete vagotomy had been done sometime previously for the treatment of duodenal ulcer, a marked response in acid secretion was observed which persisted from 8 to 10 hours after the meal. X-ray examination made at intervals following the meal demonstrated that stasis of food was present in these patients (Fig. 1). Although the cephalic or nervous phase of gastric secretion had been completely abolished by the vagotomy, the stasis of food in the stomach, as a result of the decrease in tonus and motility, brought about an exaggeration in the gastric or hormonal phase of secretion.

In 3 patients marked impairment of gastric motility was evident by x-ray examination although a positive insulin test was obtained in all, indicating that the vagotomy had been incomplete. Recurrent ulceration was not demonstrated in these patients, but they are recorded as recurrence because of the presence of ulcer symptoms, tarry stools in 1 patient, and the fact that further treatment, including x-ray therapy to the gastric fundus, subsequently produced relief. It is possible that these patients may have been suffering from erosive gastritis rather than recurrent ulcer.

Four patients with duodenal ulcer were found to have a persistent reduction in the

nocturnal gastric secretion, and x-ray examination failed to reveal the presence of active ulceration. These patients are considered to have had a recurrence because of the repeated appearance of blood in the stools, even though typical ulcer symptoms were not present. Here, also, the complication may have been a hemorrhagic gastritis or superficial gastric ulceration not disclosed by the roentgenograms.

TABLE III.—ANALYSIS OF POOR RESULTS OF VAGOTOMY AND GASTROENTEROSTOMY FOR DUODENAL ULCER

Result	*No. of cases*	*Per cent*
Proved recurrences	28	5.8
Possible recurrences	7	1.4
Gastric ulcer	2	0.4
Erosive gastritis	2	0.4
Other	4	0.8
Postoperative deaths	6	1.2
Total	49	10.0

FAILURES FOLLOWING VAGOTOMY AND GASTROENTEROSTOMY FOR DUODENAL ULCER

During the period from 1943 to 1953, 487 patients with duodenal ulcer were treated by vagotomy and gastroenterostomy in this clinic. The results were good in 400 patients (8 per cent), fair in 38 patients (8 per cent), and poor in 49 patients (10 per cent). An analysis of the poor results is given in Table III, which shows that 28 patients, or 5.8 per cent, developed a marginal gastrojejunal ulcer. Eight of these 28 patients displayed a persistent reduction in the 12 hour nocturnal gastric secretion below the normal level so it may be assumed that the vagotomy was physiologically complete and the nervous phase of gastric secretion completely abolished. Although stasis of food in the stomach with resultant hypersecretion of gastric juice of humoral origin could explain recurrent duodenal and gastric ulcers following vagotomy alone, it is not readily apparent how this could account for marginal ulceration in these patients since a gastroenterostomy had been done to prevent stasis. When, however, these 8 cases were carefully reviewed, including the operative reports and x-ray findings before and after surgery, two important facts were disclosed. It was observed first that the gastroenterostomy stomas had been placed either opposite the incisura or at the midfundus of the stomach in all cases. None appeared to be in the gastric antrums. Second, it was noted preoperatively that stenosis which produced moderate to high grade obstruction was present in all of the patients. Cicatricial stenosis of the pylorus often increases as the ulcer heals, and in many of these patients following vagotomy and gastroenterostomy, little barium could be forced through the pylorus. In view of the recent experiments by Rigler and his associates in this laboratory whereby a hypersecretion of gastric juice of humoral origin was produced in dogs by partial obstruction at the pylorus, an exaggerated antral phase of secretion might be expected in these patients since all of them showed a considerable degree of pyloric stenosis. Reference has previously been made to the experimental studies of Zubiran and his associates in which a sustained increase in gastric secretion of humoral origin was produced in Heidenhain pouch dogs by means of a high lying gastroenterostomy. Most of these patients had been operated upon early in our experience with vagotomy, and no special attention was directed toward positioning the gastroenterostomy stoma near the pylorus. This remained the case until 1952, following the physiologic observations made in the experimental animals. It has also been pointed out that the high lying gastroenterostomy does not overcome

TABLE IV.—RELATION OF RECURRENCE OF ULCER TO NOCTURNAL SECRETION AND INSULIN RESPONSE BEFORE AND AFTER VAGOTOMY AND GASTROENTEROSTOMY (28 CASES)

12 hr. postop. night secretion in mEq.	*No. of recurrences*	*Positive response to insulin hypoglycemia*	*Negative test*
100 plus	2	2	0
80 to 100	2	2	0
60 to 80	0	0	0
40 to 60	6	6	0
20 to 40	1	1	0
0 to 20	8	3	5
	19		
Cases insufficient data.	9		
	28		

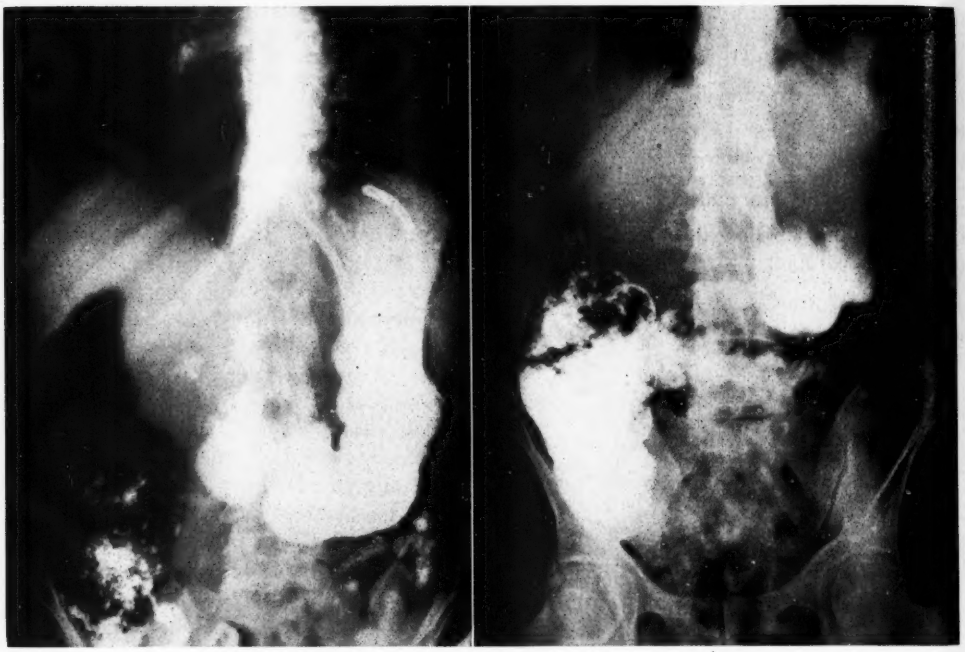

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FIG. 1. Patient P. L., duodenal ulcer treated by vagotomy alone in 1945. a, Barium meal is shown in the stomach 2 hours after ingestion; b, 26 hours later.

the stasis that exists in the antrum following vagotomy to the main stomach in Heidenhain pouch dogs. Therefore, it is readily apparent that stasis of food in the gastric antrum of these patients could lead to a hypersecretion of gastric juice of humoral origin as a result of a combination of factors. These include pyloric stenosis, decreased gastric motility as a result of the vagotomy, and a high lying gastroenterostomy which fails to empty the stomach adequately and which, in itself, causes a hyperfunction of the antral phase of secretion. A hypersecretion of gastric juice of humoral origin in experimental animals has been found as potent in producing ulceration as one of nervous origin.

In 11 of the 28 patients in whom marginal ulcers developed after vagotomy and gastroenterostomy for duodenal ulcer, there was little or no reduction in the 12 hour nocturnal gastric secretion, and all of these patients showed a positive response to insulin hypoglycemia. The poor results in these patients may probably be accounted for, chiefly, on the basis of incomplete vagotomy although in these cases, also, a high lying gastroenterostomy may have been a contributory factor. There were 9 patients with proved recurrence in which the secretory data were insufficient to permit analysis.

Seven patients or 1 per cent are recorded as having had a possible recurrent ulcer because of mild recurrent symptoms, but without definite objective evidence of ulceration. Several of the patients in this group were heard from only by letter describing their symptoms.

Two of the 487 patients with duodenal ulcer treated by vagotomy and gastroenterostomy subsequently developed a benign gastric ulcer after intervals of 1 and 7 years following the original operation. Two patients developed severe antrum gastritis 2 and 3 years following surgery. In these 4

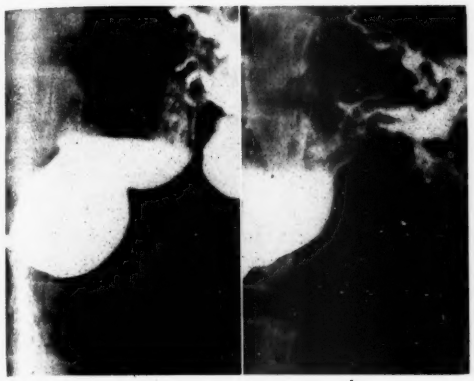

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FIG. 2.

FIG. 2. Patient C. F., vagotomy and gastroenterostomy December 10, 1948, for recurrent duodenal ulcer. X-ray examination April, 1954. a, Stenosis of the pylorus is demonstrated with retention of food in the antrum of the stomach because of the high lying gastroenterostomy revealed in b.

FIG. 3. X-ray examination revealing persistence of barium in the stomach of patient C. F. 12 hours after figure 2.

FIG. 3.

patients, persistent reduction in the 12 hour night secretion and negative response to insulin hypoglycemia indicated that the vagotomy had been complete and the nervous phase of gastric secretion had been abolished. It seems probable that the failures here were also due to a stasis of food in the stomach, resulting from the decreased motility after vagotomy and the presence of the high lying gastroenterostomy. In each of these cases, the gastrojejunostomy stoma was in the fundus of the stomach. A clinical history of 1 of these patients follows.

C. F., Unit No. 458237, a 59 year old white male, was first admitted to the hospital in November 1948, complaining of ulcer type distress of 31 years' duration. He had previously suffered a perforation which was treated by closure and a gastroenterostomy. Subsequently, a marginal ulcer and a gastrojejunal colic fistula developed. This was repaired and the patient was well until several months before admission to this hospital when he developed recurrent epigastric distress which was not relieved by milk, cream, or alkalies. X-ray examination revealed an ulcer crater in a deformed duodenal bulb without obstruction. The preoperative 12 hour nocturnal gastric secretion averaged 2,120 cubic centimeters with a free acid concentration of 93 clinical units and a calculated 12 hour output of free hydrochloric acid of 197 milliequivalents. This compares with 15 to 20 milliequivalents of free hydrochloric acid put out in the 12 hour period by normal people. On December 10, 1948 the previous gastroenterostomy was taken down and a transabdominal supradiaphragmatic vagotomy and posterior gastroenterostomy were performed. The postoperative 12 hour nocturnal gastric secretion measured 970 cubic centimeters with 22 clinical units of free acid or an output of 20 milliequivalents of free hydrochloric acid, representing a 90 per cent reduction from the preoperative level. Following this operation the patient complained of persistent epigastric fullness, belching, and occasional diarrhea. At times he had a burning epigastric distress, not relieved by milk or alkalies. In January 1950, he was readmitted to the hospital for gastric secretory studies. The 12 hour nocturnal gastric secretion measured 350 cubic centimeters with no free acid. The response to insulin hypoglycemia was negative. However, he continued to complain of intermittent, burning distress in the epigastrium, fullness, and belching. He was again examined in September 1951, when his 12 hour nocturnal gastric secretion measured 500 cubic centimeters with a free acidity of 36 clinical units or an acid output of 18 milliequivalents, representing a persistent reduction from the prevagotomy level. The

secretory response to insulin hypoglycemia remained negative. He was again readmitted to the hospital in April 1954, complaining of postprandial fullness and vague epigastric distress relieved only by alkalies. X-ray examination revealed stenosis of the pylorus with marked retention of barium in the gastric antrum distal to the gastroenterostomy site (Fig. 2) which was located somewhat high on the greater curvature of the stomach. A barium motor meal revealed retention of food in the stomach up to 12 hours (Fig. 3). The 12 hour nocturnal gastric secretion measured 450 cubic centimeters with 28 clinical units of free acid or an acid output of 13 milliequivalents in 12 hours. The secretory response to insulin hypoglycemia was negative. On March 17, 1954 a partial gastrectomy was performed, removing the gastric antrum. The pathologic diagnosis of the specimen was chronic, erosive gastritis of the antrum. The patient has remained well since this last operation and postoperative 12 hour nocturnal gastric secretions have failed to reveal any free acid.

CONCLUSIONS

1. Complete gastric vagotomy may produce a prolongation of the antrum or humoral phase of gastric secretion in experimental animals because of stasis of food in the stomach.

2. A high lying gastroenterostomy produces stimulation of gastric secretion in experimental animals, but this does not occur if the gastroenterostomy stoma is located in the antrum near the pylorus.

3. The increase in gastric secretion due to prolongation of the humoral mechanism of secretion after vagotomy is prevented by a gastroenterostomy with the stoma in the antrum close to the pylorus, but not if a gastroenterostomy stoma is made higher up on the fundus of the stomach.

4. Analysis of failures in the treatment of duodenal ulcer by vagotomy alone and by vagotomy combined with gastroenterostomy disclosed that stasis of food in the stomach and a high lying gastroenterostomy were important factors in many patients.

5. Of 158 patients with duodenal ulcer treated by vagotomy alone, 5 subsequently developed a new gastric ulcer and 2 developed erosive hemorrhagic gastritis. Experimental data suggest that these lesions were produced by a hypersecretion of gastric juice of humoral origin as a result of gastric stasis due to impaired gastric motility and to pyloric stenosis.

6. Eight patients with duodenal ulcer treated by vagotomy and gastroenterostomy subsequently developed gastrojejunal ulcers, although the nocturnal gastric secretion had been reduced to normal levels, and in 5 of these patients, the secretory response to insulin hypoglycemia was negative. It seems probable that the stoma ulcers in these patients were due to antrum hyperfunction, resulting from the high lying gastroenterostomy with associated pyloric stenosis and, possibly, also decreased motility as a result of the vagotomy.

7. Two patients developed a new gastric ulcer and 2 developed erosive, hemorrhagic gastritis following vagotomy and gastroenterostomy for duodenal ulcer. A high lying gastroenterostomy with the stoma in the fundus of the stomach was present in all.

8. The experimental and clinical evidence presented indicates that the stoma should be placed in the antrum within 4 or 5 centimeters of the pylorus whenever a gastroenterostomy is done along with vagotomy in the surgical treatment of duodenal ulcer.

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THE IMPORTANCE OF TECHNIQUE IN CHOLECYSTECTOMY

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IN THE PRESENT ERA we are experiencing many advances in surgery, a large number of which are so spectacular that we tend to overlook some of the deficiencies in our regular day's work. In the past decade developments in cardiovascular surgery have gone beyond our anticipation. Chemotherapy and progress in anesthesia have been important in the reduction of postoperative morbidity and mortality. In biliary tract surgery vitamin K has enabled us to control the bleeding tendency in jaundiced patients so efficiently that it is no longer the hazard it once was. Surgeons as a group are justified in telling patients that the scope of surgical therapy has been greatly increased in recent years and that it has become more safe than ever before. Surgical progress is to be made by the continual evaluation and studies of our methods, procedures, and techniques. We should not be content with improvement alone so long as our results leave something to be desired. The more frequently a procedure is employed the greater is the need for rendering it as simple and as safe as possible for patients.

Operations upon the biliary tract are in this category. Gallstones are the basis for most of those conditions that are treated surgically. It is estimated that 10 per cent of the adult population of this country have gallstones, and while they may produce no symptoms in some patients biliary calculi cause a great deal of disability. The operative procedures most frequently employed are cholecystectomy, cholecystostomy, and choledochotomy. The first to be developed as a planned procedure was cholecystostomy which was described by John S. Bobbs (1) in 1869 and further elaborated upon by Marion Sims (4) in 1878. Shortly thereafter, in 1880 in Germany Langenbeck began to do and advocate cholecystectomy for gallstones. In 1890 Kümmell demonstrated the successful removal of stones from the common duct by choledochotomy. Less than 90 years have elapsed since cholecystostomy was introduced as the principal operative procedure for gallbladder disease including cholelithiasis. In this period surgery has become a much more effectual means of therapy for a wider range of man's ills. Although we do not have a ready means for determining the actual number of operations that are performed daily in this country, we believe operations upon the biliary tract are among the most frequent. In The New York Hospital-Cornell Medical Center with a 1,000 bed capacity embracing the common divisions of medicine, there are approximately 10,000 surgical operations performed each year. About 500 or 5 per cent are for biliary tract disease. Cholecystectomies for cholecystitis with cholelithiasis constitute over 90 per cent of the operations for biliary tract disease.

It is reasonable to assume that this medical center hospital is quite representative of the hospitals and total general hospital beds of the country as a whole. If such be true, then cholecystectomy is probably one of the most frequently performed operations in this country. It follows also that, in all likelihood, more surgeons throughout the land perform cholecystectomy than any other operation. It is quite proper, therefore, in this era of rapid advancement in surgery that, from time to time, we consider in a critical manner the status of those procedures which are most frequently employed by the greatest number of surgeons to determine whether or not they

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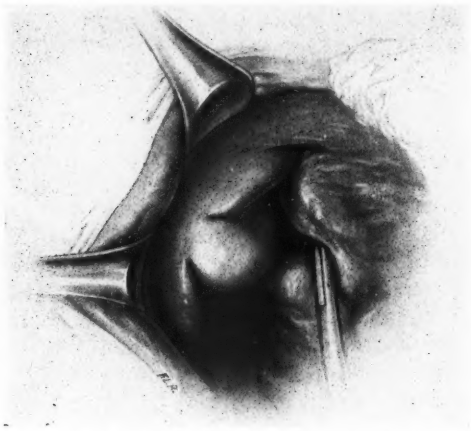


FIG. 1. In acute cholecystitis the omentum is adherent to the acutely distended, inflamed gallbladder.

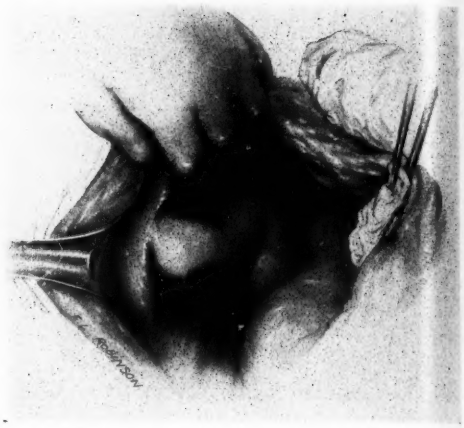


FIG. 2. The omentum and transverse colon are reflected from the gallbladder.

are being done as well as they might and with as little risk as possible to the patient.

In an attempt to accomplish this objective it is essential that the over-all picture of biliary tract surgery for the entire country be kept in mind. This survey should include the smallest as well as the largest hospitals where these operations are performed, and those who operate upon the biliary tract once in a month as well as the surgeons who perform several such operations daily, and all the variations between these two extremes. Thus, while the medical centers report the largest case series, it does not necessarily follow that they do the greater proportion of surgery on the biliary tract; actually the indications are that it is done in a great number of smaller hospitals by a larger number of surgeons with a wider range of capability. The surgical experience reported in our medical journals over the past 10 years is encouraging. The incidence of postoperative complications and the mortality have been reduced. There is little doubt that the same trend has held for the country as a whole. However, one may seriously question whether or not the results are as good beyond those centers that commonly publish their experiences.

Each year we admit to the surgical service of The New York Hospital-Cornell Medical Center patients who have been operated upon previously, usually for gallstones, who have either new and severe symptoms or persistence or a recurrence of symptoms following the primary operation. The two most frequent causes of the apparent failure of the original surgical procedure are common duct injury and residual cystic duct remnant. Both of these are the result of technical errors. It is highly desirable that they be reduced to a minimum.

The first of these is by far the most important. Injury to the common duct that leads to stricture and obstruction impairs the health and reduces the life expectancy far beyond that of stones in the biliary tract. Although there are optimistic reports of some of our leading surgical clinics concerning the successful correction of traumatic injuries to the common duct and their sequelae, there is to be observed in the experience of all surgeons who have undertaken this type of reconstructive work examples in which the survival time following injury has been less than 5 years despite heroic surgical measures. Injuries to the common duct during cholecystectomy continue to occur. The prevention of these accidents, for indeed no one intends to injure the common duct, must depend upon the continuous and further education

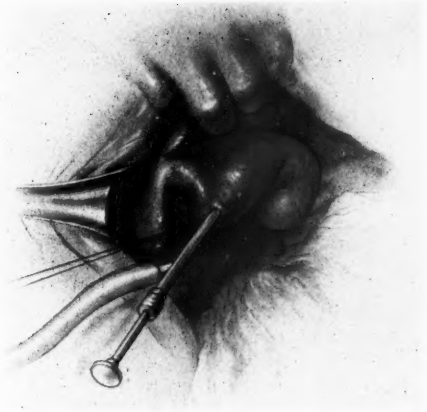


FIG. 3. A generous incision enables the assistants to provide adequate exposure for the surgeon. In the presence of a distended, acutely inflamed gallbladder the organ should be decompressed, as indicated in this illustration, as a preliminary step to approaching the cystic duct.

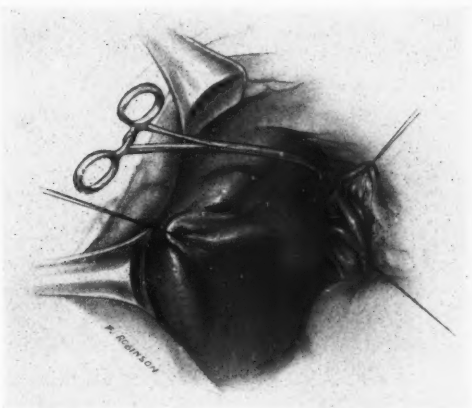


FIG. 4. The peritoneum has been incised parallel to the common duct in the apparent area of its junction with the cystic duct. The cystic duct is dissected sufficiently to pass a silk ligature about it for identification purposes. The dissection is then extended cephalad and laterally toward the gallbladder wall to expose the cystic artery.

of all who attempt cholecystectomy. It is most important for those who operate upon the biliary tract to have a true realization of the seriousness of common duct injury. In seeking to find out from the operator the exact details of the operative procedures in which the common duct was injured, I have been impressed with the following: (1) The common duct has been mistaken for the cystic duct and divided because of inadequate demonstration of the junction of the two. (2) Injury to the cystic or hepatic artery has resulted in hemorrhage that has obscured the operative field. Blind clamping and ligating of unidentified structures have resulted in complete or incomplete obliteration of the common duct. (3) In no instance have I talked with a surgeon who has injured the common duct while removing the gallbladder by dissecting it from the fundus toward the cystic duct. (4) About half of those who injured the common duct were "casual" gallbladder surgeons; the remainder were individuals of considerable operative experience, and it is difficult to understand that they would divide any structure without being quite certain of its correct identity.

These observations and the reported experiences of others equally concerned with the prevention of common duct injuries are the basis for the following recommendations to those who would perform cholecystectomy: (1) Be aware of the seriousness of common duct injury. (2) Be familiar with the normal anatomy and congenital anomalies of the biliary system and its associated vascular system. (3) Allow plenty of time for the operation so that deliberate dissection will facilitate unquestionable identification of all structures. (4) Employ generous incisions to enable your assistants to provide easy and adequate exposure. (5) Divide no structure until it has been identified beyond any question of doubt. (6) Perform cholecystectomy by first dissecting the gallbladder from its bed and then dividing the cystic duct only after demonstrating its junction with the common duct by the following steps: (a) incision of the peritoneum parallel to the common duct in the apparent area of its junction with the cystic duct; (b) the identification of the cystic duct and its dissection sufficient to enable one to pass a silk ligature about it; (c) extension of the dissection cephalad and laterally toward the wall

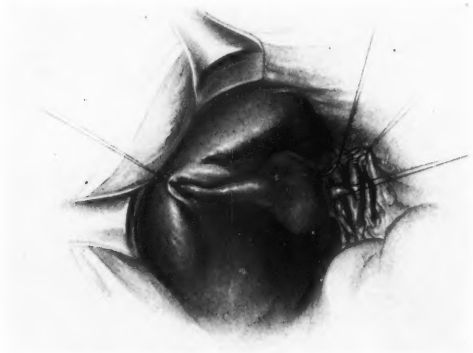


FIG. 5. The cystic artery is dissected to its junction with the gallbladder and temporarily ligated by setting one knot in the silk ligature.

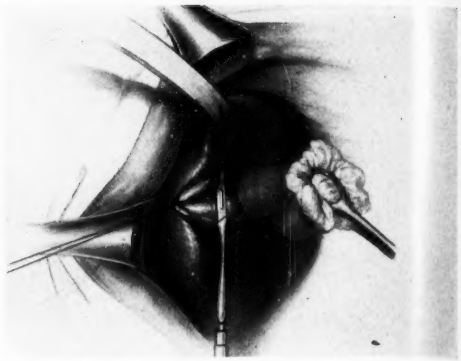


FIG. 6. Following the temporary ligation of the cystic artery, the peritoneum of the gallbladder is incised 1 centimeter from its junction with the liver anteriorly.

of the gallbladder to expose the cystic artery which is dissected free a sufficient distance to permit a silk ligature to be passed about it and set by one knot, preferably just before it branches within the wall of the gallbladder; (d) incision of the peritoneum over the gallbladder 1 centimeter from its junction with the liver, and dissection of the gallbladder from its liver bed from the fundus toward the cystic duct; (e) as the ampulla of the gallbladder is approached, division of the branches of the cystic artery as they enter the wall of the gallbladder and permanent fixation of the cystic artery; (f) then dissection of the cystic duct down to its true junction with the common duct and division ½ centimeter from it.

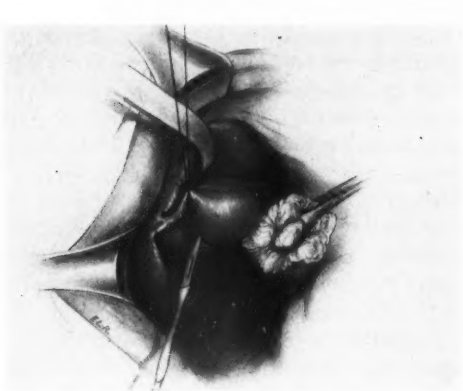


FIG. 7. After incising the peritoneum anteriorly, a corresponding incision through the peritoneum is made inferiorly.

It is my opinion that the most common error during cholecystectomy is committed at that point where the operator clamps and divides what he believes to be the cystic duct but is actually the common duct or the right hepatic artery. If the method of cholecystectomy as outlined is followed in meticulous detail, it is believed that hemorrhage which obscures the field will rarely be encountered, furthermore, that there will be less likelihood of mistaking the right hepatic artery for the cystic duct. When the gallbladder has been dissected from its bed with the cystic duct intact it is quite easy to follow it to its true junction with the common duct. This provides a much better opportunity to visualize the cystic duct in its entirety than when one attempts to dissect with the gallbladder in its fixed location. The cystic duct frequently joins the common duct 1 to several centimeters from the distal end where it turns from its parallel position to enter the ampulla of the gallbladder. It is not uncommon for it to enter the common duct posteriorly rather than from the anterior and lateral aspect.

In many surgical textbooks there are illustrations indicating that the gallbladder after dissection from its bed can, by gentle traction, cause a tenting of the common duct so that a ligature or clamp may easily encircle

it. It seems that only the most unobservant would injure the duct under such circumstances with the junction under direct vision. The well trained and careful surgeon may remove the gallbladder completely and with safety regardless of the method he employs. Certainly the surgeon is of greater importance than the method. In my close association with surgeons in training over the past 25 years I have repeatedly said that it probably made little difference whether the gallbladder was removed from the fundus toward the cystic duct or in retrograde fashion. Indeed, from my experience with young men in training in a medical center, I have no justification for changing my opinion. However, based on the information I have gained from those surgeons who have injured the common duct, it now seems to me that cholecystectomy performed by first dissecting the gallbladder from its bed and then demonstrating the true junction of the cystic with the common duct before dividing the cystic duct would result in fewer accidents.

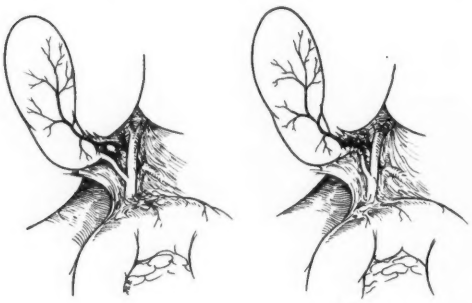
The cystic duct should be secured and divided within 5 millimeters of its junction with the common duct. If it is ligated flush with the wall of the common duct that is indurated, as is frequently seen associated with an inflammatory process, then it may be sheared off. The result is a defect which allows the escape of bile or requires placing sutures in the wall which may diminish the lumen of the common duct.

If more than a few millimeters of the cystic duct remain, the remnant may enlarge and be the site of future gallstones. An enlarged cystic duct remnant containing stones may give rise to symptoms indistinguishable from those of a gallbladder containing stones. It may be the site of acute inflammatory processes. Common duct stones frequently accompany calculi in a cystic duct remnant. To leave a cystic duct remnant that may cause persistent or recurrent symptoms is to do an incomplete operation.

In those patients who have had recurrent inflammatory episodes of the gallbladder involving the lymph gland which is commonly found between the cystic artery and the cystic duct, it is easy to understand how there may be scarring and fibrosis about these structures. Thus, the two are held closely together and sometimes are not readily dissected apart. It may be very tempting to the unsuspecting surgeon to clamp these two structures, divide, and ligate them together without first isolating the cystic duct from the adjacent cystic artery and then dissecting it down to the true junction with the common duct (Figs. 4 and 5). If the cystic duct has its true junction with the common duct medially and posteriorly, and nearer the ampulla of Vater than is usual, it is less likely to be recognized if the cystic duct and cystic artery are ligated together (Fig. 9).

Attention was called to the significance of cystic duct remnants by Florecken in 1912. Since then the series of cases reported by Morton and by Peterson have further emphasized the clinical picture that may follow if the cystic duct is not properly removed when a cholecystectomy is performed. Until

FIG. 8. The gallbladder is dissected from its liver bed from the fundus toward the cystic duct. As the ampulla of the gallbladder is approached the branches of the cystic artery as they enter the wall of the gallbladder are divided and the cystic artery is permanently secured. The cystic duct is then dissected down to its true junction with the common duct. It is secured with a ligature of catgut and a transfixing suture of silk and divided ½ centimeter from the common duct. The gallbladder is then removed.



a b

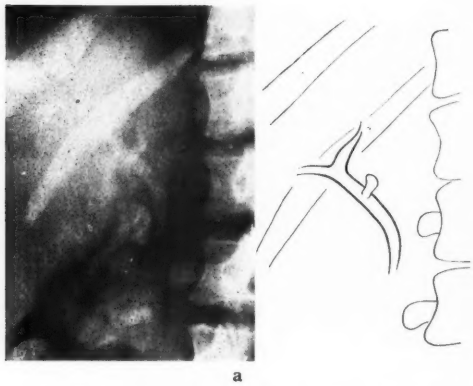
FIG. 9. Drawings demonstrating: a, a lymph gland that is commonly found between the cystic artery and cystic duct and b, scarring and fibrosis following inflammatory reaction which often results in these structures being held close together.

recently few cystic duct remnants were demonstrated other than by operation. Thus, many patients were encouraged to tolerate their symptoms, and operation was not advised because visualization of the common duct and the cystic duct remnant was rarely accomplished.

In 1953, cholografin (a 20 per cent adipylbis 3 amino 2:4:6-triiodo benzoic acid) was made available in this country for intravenous cholangiography. Visualization of the common bile duct in patients whose gallbladders have been removed can be accomplished in a high percentage of instances, in the absence of jaundice or impaired liver function, and has become an important method (3) in demonstrating a suspected cystic duct remnant.

At The New York Hospital-Cornell Medical Center we have successfully visualized the common duct by this method in over 350 patients in whom this condition was indicated. Included in this experience are 121 patients with persistence or reappearance of symptoms after cholecystectomy. For the most part, these symptoms have been right upper quadrant or midepigastric pain, nausea, vomiting, and intolerance for fatty food or large meals. Some of these patients have had varying degrees of jaundice.

Of these 121 patients subjected to intravenous cholangiography because of symptoms after cholecystectomy, 100 were women and 21 were men. The age range was from 23 to 29 years. The common duct was satisfactorily visualized in 105 or 86.8 per cent. The most frequent evident cause for nonvisualization was jaundice and impaired liver function. Abnormalities of the biliary ductal system were demonstrated in 40 patients, including: cystic duct remnant in 18, calculi in 11, and adhesive bands and strictures in 11. In 20 patients the only abnormality demonstrated was a dilatation of all or a portion of the ductal system of 7 millimeters in diameter or greater. Fifteen of the 121 patients had no abnormality of the ductal



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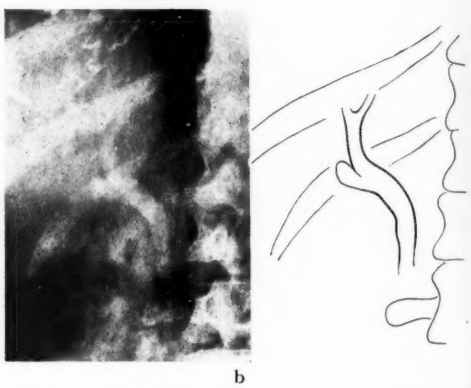

b

FIG. 10. a, Intravenous cholangiogram of a female, aged 30, demonstrating residual cystic duct remnant. b, Intravenous cholangiogram of a female, aged 65, demonstrating residual cystic duct remnant.

system. In a solitary, obese individual without signs of jaundice and with normal liver function the common duct was not visualized. Twenty-six patients were found by additional examinations to have duodenal ulcer, hiatus hernia, pancreatitis, or renal disease that might wholly or in part be the cause of their symptoms.

It is our opinion that intravenous cholangiography provides an additional means of demonstrating cystic duct remnants and that greater attention will be directed to the clinical symptoms associated with it. Meticulous attention to the technical details of cholecystectomy would seem a proper approach in reducing its incidence.

SUMMARY

Operations upon the biliary tract are among the most frequently performed in hospitals of the United States. Of these, cholecystectomy is by far the most common procedure. Probably there are more surgeons performing this operation than any other. The surgical therapy of biliary tract disease has been a development of the past 90 years; it has been highly successful. Each decade since its introduction has seen an extension of its application with ever increasing safety to patients. Reports from many hospitals attest to the low morbidity and low mortality rate following surgery.

However, those who operate upon the biliary tract should strive to prevent two postoperative conditions. The first and more serious is injury to the common duct and the second is leaving a remnant of the cystic duct. It is suggested by the author that individual identification and dissection of the cystic duct and cystic artery, with temporary ligation of the latter followed by the removal of the gallbladder from the fundus toward the cystic duct and the unequivocal demonstration of the true junction with the common duct would enable even the less expert to do a complete cholecystectomy with greater safety.

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THE MYENTERIC PLEXUS IN REGIONAL ENTERITIS: A STUDY OF THE NUMBER OF GANGLION CELLS IN THE ILEUM IN 24 CASES

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THAT QUANTITATIVE CHANGES OCCUR in the myenteric plexus in association with certain diseases of the gastrointestinal tract is no longer a matter of conjecture. Robertson and Kernohan, in 1938, were the first in this country to suggest that an absence of ganglion cells exists in the myenteric plexus of persons suffering from congenital megacolon. Ten years later, Whitehouse and Kernohan found that in all 11 cases of congenital megacolon which they studied there was an absence of ganglion cells in the myenteric plexus of the terminal portion of the colon. Storsteen, Kernohan, and Bargen studied 25 cases of chronic ulcerative colitis, "a disease entity representing the very antithesis of congenital megacolon, namely, overactivity," and compared their findings with those from study of an equal number of controls. They concluded that a threefold increase was present in the number of ganglion cells in the myenteric plexus of persons suffering from chronic ulcerative colitis. Deficits in the number of ganglion cells have been described in cardiospasm by Lendrum, and the findings of Belding and Kernohan lend support to the theory that congenital hypertrophic pyloric stenosis occurs on a neurogenic basis.

The similarity between chronic ulcerative colitis and regional enteritis with respect to anatomic distribution of involvement and pathologic and clinical manifestations suggests that the two entities are closely related. In view of the finding that chronic ulcerative colitis is associated with an overabundance of ganglion cells, coupled with reports in the medical literature claiming beneficial effects from vagotomy in both chronic ulcerative colitis and regional enteritis, we decided that a quantitative study of the ganglion cells of Auerbach's plexus in regional enteritis should contribute to our knowledge of the disease.

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Abridgment of thesis submitted by Dr. Davis to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

NERVE SUPPLY OF SMALL INTESTINE

Since 1862, when Auerbach described the enteric plexus which bears his name, a great mass of literature has accumulated concerning the structure and function of this interesting detail of anatomy. Investigators, nevertheless, have been slow to agree on the significance of the various portions of the plexus as related to function in normal intestine. In general, the nerve supply to the small intestine consists of two systems, one extrinsic and the other intrinsic.

Extrinsic system. Nerves entering the intestine from without are made up of parasympathetic and sympathetic components. The cell bodies of the parasympathetic fibers are located in the dorsal efferent nucleus of the vagus, the fibers are preganglionic medullated fibers destined to synapse with terminal ganglia located in the myenteric plexus. Ganglion cells of the myenteric plexus are the nutritive cell bodies for the postganglionic components of the vagus nerves and, hence, must be considered a part of the parasympathetic system. Sympathetic fibers arise in the

intermediolateral cell column of the lower thoracic and upper lumbar segments of the spinal cord and, as preganglionic fibers, synapse in vertebral, celiac, or superior mesenteric ganglia. Postganglionic components continue as nonmedullated fibers to terminate directly on the structures innervated. Nerves to the small intestine, derived from the plexuses around the celiac and superior mesenteric arteries, course through the mesentery in close relationship with the mesenteric vessels and with them pierce the intestinal wall. The vagal fibers are less intimately associated with the vessels than the sympathetic nerves.

Intrinsic system. Located in the intestinal wall, the intrinsic nervous system consists of an extensive interlacing feltwork of nerve cells and their interconnecting fibers which are continuous from the upper limits of the esophagus to the internal sphincter muscle of the anus. Three well defined plexuses have been identified: (1) the subserous plexus, considered by Hill to be largely afferent in function; (2) the myenteric plexus (plexus of Auerbach); and (3) the submucous plexus (plexus of Meissner). The myenteric and submucous plexuses consist of groups of nerve cells connected by bundles of fibers; these fibers are both extrinsic and intrinsic in origin. Meissner's plexus, which is much smaller than Auerbach's plexus, is in the submucosal layer immediately beneath the muscularis mucosae. The latter consists of groups of ganglion cells and interlacing bundles of fibers placed between the outer longitudinal and inner circular muscle coats of the intestinal wall.

Dogiel, using the supravitum methylene blue technique, described three distinct morphologic types of cells in the myenteric plexus which he chose to designate as types 1, 2, and 3. He was of the opinion that the cells classified as type 1 were motor neurons whose axons terminated on smooth muscle cells. To type 2 cells he ascribed a sensory function because of their long dendrites reaching up to the mucosa. No definite suggestion was made as to the significance of type 3 cells. Certain observers have been able to differentiate Dogiel's cells readily whereas others have concluded that all of the ganglion cells of the myenteric plexus are of a single type. Dogiel described pericellular capsules around the ganglion cells but neither Hill nor Kuntz have been able to duplicate his observation.

In addition to ganglion cells and bundles of fibers in the myenteric plexus, a complex, interlacing network of supportive cells, commonly referred to as the "interstitial cells of Cajal," is closely associated with nerve elements. These cells are irregularly shaped, smaller than ganglion cells, and their cytoplasm which is usually scant is frequently vacuolated. Nuclei vary from round to oval and usually it is not possible to identify a definite nucleolus. Tiny varicose appendages arise from the cell bodies to intermingle among the nerve cells and fiber bundles of the plexus as well as the processes of other similar cells. Thus, they form a delicate but dense network of fibers within the plexus. The nature of these cells has been a source of divergent opinion for many years; some anatomists consider them to be merely connective tissue cells whereas others think of them as true nervous tissue elements. Hill concluded that these cells were similar to the microglia of the central nervous system.

Function of the myenteric plexus. The main function of the myenteric plexus is to relay stimuli to the musculature of the intestine and to co-ordinate its movements. The vagus, whose terminal fibers connect with ganglion cells of the myenteric plexus, augments movements whereas the sympathetic nerves exert an inhibitory influence. Meltzer and Auer described three kinds of motor phenomenon in the small intestine: (1) pendular movements which are rhythmic and swaying motions which are concerned with the mixing of food, (2) peristaltic movements effective in propulsion of intestinal contents, and (3) the peristaltic rush, a fast running movement extending over the whole or a large part of the small intestine. Pendular movements have been shown to be myogenic. Co-ordi-

nated peristaltic movements, on the other hand, depend on the integrity of the intrinsic nervous system, namely the myenteric plexus. Peristaltic rushes depend on the extrinsic nerve supply and are abolished after vagotomy. Alvarez described two general functions of the myenteric plexus whereby coordinated intestinal movements are brought about. One function, he claimed, is the "prevention of spasmodic contraction" and stated that it has been known for many years that smooth muscle, devoid of its ganglionic centers of control, tends to contract into a firm mass such as occurs in the unyielding muscle rings seen in megacolon and cardiospasm. A second function, which he preferred to call "another type of quieting effect," is brought about by activity of both extrinsic and intrinsic systems. This quieting effect regulates the response of smooth muscle so that it does not react violently and excessively to constantly arriving stimuli. The diarrhea frequently encountered after section of extrinsic nerves is explained on the basis of loss of this function.

Investigative studies employing degenerative section of extrinsic nerves, spinal anesthesia, and the response of intestinal muscle to various drugs before and after deganglionation in isolated strips have given much information about anatomy and function of the myenteric plexus. At present, however, there are no known laboratory methods for the determination of the deviation from normal that may be expected secondary to an increased number of ganglion cells in the myenteric plexus. Studies of this sort, if possible, could serve to influence our present concept of chronic ulcerative colitis and regional enteritis.

MATERIAL AND METHODS

Twenty-five cases of regional enteritis and 25 controls were selected for study. The specimens used as controls were obtained from consecutive necropsies in cases in which the terminal ileum, ileocecal valve, and cecum were clinically, grossly, and microscopically normal. The specimens from patients with regional enteritis were obtained as a result of therapeutic surgical operations in which the surgeon had resected the ileum well above the site of disease and included the ileocecal valve in the specimen. Specimens from patients with regional enteritis treated previously with roentgen therapy were excluded from study. When the sections were examined, 1 case of regional enteritis was rejected because of severe distortion and destruction of the myenteric plexus secondary to inflammation. One case from the control series also was not accepted because of the difficulty in obtaining anything but tangential sections. Specimens from 24 cases of regional enteritis and 24 controls, therefore, were studied.

A reasonably equal distribution between the two sexes prevailed in each group; 10 males and 14 females had regional enteritis; 13 males and 11 females were in the control group. The difficulty encountered in obtaining controls from the same age group as the patients with regional enteritis led us to abandon this effort as impractical. It was attempted, however, to select patients with regional enteritis whose ages compared favorably, percentagewise, with the natural occurrence of the disease. Three patients were aged 20 years or less, 6 were more than 40 years old, and the majority, 15, were from 21 to 40 years of age.

All gross specimens from the cases of regional enteritis and from the controls were fixed in a solution of 10 per cent formalin for a minimum of 30 days preliminary to the cutting of tissue blocks. Four blocks of tissue were cut in the transverse direction at different levels (Fig. 1) from each specimen and trimmed so that each measured exactly 2 centimeters in length. Three blocks were cut at various levels in the portions of ileum showing gross disease and the fourth was cut from normal-appearing bowel above the diseased area. Blocks were cut from control specimens at levels corresponding to the site of blocks cut from diseased specimens. The distance from the ileocecal valve and the circumference of the intestine at the level of each block was carefully measured and recorded.

All blocks were imbedded in paraffin and cut in transverse sections measuring 8.0 microns in thickness. Special care was taken to mount each block on the microtome stage so that sections would be cut at right angles to the lumen of the bowel. Fragmented and tangential sections were recut until satisfactory for the counting of ganglion cells.

In selecting the staining method most suitable for the counting of ganglion cells the following stains were used: cresyl violet, hematoxylin and eosin, modified Bodian, van Gieson's for connective tissue, and theonine. Cresyl violet was by far the most satisfactory as it exhibited a specific affinity for all the central portions of ganglion cells, namely, the cytoplasm, nucleus, and nucleolus. With this stain ganglion cells stood out in bold relief between the lighter staining muscular coats, and other structures, such as nerve bundles, supportive cells, and inflammatory cells, were readily distinguishable. Hematoxylin and eosin proved to be of general value only but this method was of great aid in orientation when the appearance of various structures after use of the various special stains was compared. The modified Bodian method of silver impregnation showed nerve fibers and bundles satisfactorily but was definitely inferior to cresyl violet in its ability to show the central anatomy of ganglion cells. The elastic van Gieson stain was not satisfactory for actual counts but showed connective tissue well. Theonine produced a color differential similar to cresyl violet but with considerably less contrast and uniformity than the latter and, furthermore, slides stained with theonine faded rapidly. On the basis of the foregoing experience, all sections used for the counting of ganglion cells were stained with cresyl violet.

Rigid criteria were established with regard to identification of ganglion cells. Obviously, an accurate estimate could not be determined by counting all cells, including those in which only a fringe of their cytoplasm was cut across, because such cells have no specific identifying features. It was decided, therefore, to count only those cells in each section which had a nucleus, nucleolus, and an identifiable rim or cytoplasm. No effort was made to differentiate between Dogiel's cell types 1 and 2, and if doubt existed as to the identity of a cell it was not counted. No particular attention was paid to the presence or absence of pathologic changes in individual nerve cells, plexus, or fiber bundles; however, the swollen appearance of ganglion cells in regional enteritis, the hyperplastic appearance of the plexus in general, and the great abundance of fiber bundles did not escape notice.

One problem was how best to express the findings of such a study, yet make adequate allowances for certain factors which could possibly influence the accuracy of results. On the assumption that dilatation, thickening, or circumferential shrinkage does not alter the quantity of ganglion cells present but merely condenses or disperses them as the case may be, it was decided to estimate as accurately as possible the total number of ganglion cells in a complete cross section of intestine 8.0 microns thick. Knowing the circumference of the ileum at the serosa and having determined the distance from serosa to myenteric plexus by actual measurement under the microscope, by means of the formula $C = 2 \pi R$, we were able to compute the circumference of the myenteric ring for each section. The number of ganglion cells in the myenteric plexus was counted in each 2 centimeter strip of intestinal wall and divided by 2 to obtain the number of ganglion cells per centimeter. By multiplying the ganglion cell count per centimeter by the circumference of the myenteric ring, we estimated the total number of ganglion cells in a complete cross section of ileum measuring 8.0 microns in thickness.

For each case of regional enteritis the sex and age of the patient, duration of symptoms, length of ileum involved, and the type of disease, whether localized or segmental, whether complicated by fistula or intestinal obstruction, were recorded. The degree of intestinal obstruction was graded 1 to 4; grade 1 was minimal obstruction, grade 2,

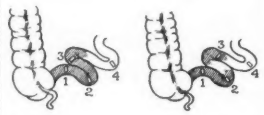
Section	Regional enteritis		Controls
	Localized	Segmental	
			
1	5.3 cm.		5.4 cm.
2	13.4 cm.		12.9 cm.
3	24.1 cm.		24.0 cm.
4	42.3 cm.		39.8 cm.

FIG. 1. Average sites from which blocks of tissue were cut from the ileum in 24 cases of regional enteritis and 24 controls; measurements in centimeters indicate distance proximal to the ileocecal valve.

moderate, grade 3, severe but incomplete, grade 4, complete. Obstruction, grade 4, was not encountered. Additional data included pathologic reports, location, circumference, count of ganglion cells per centimeter, and per circumference (estimated) at the level of each section. Data collected on the controls included the age and sex of the patient and cause of death as determined by necropsy.

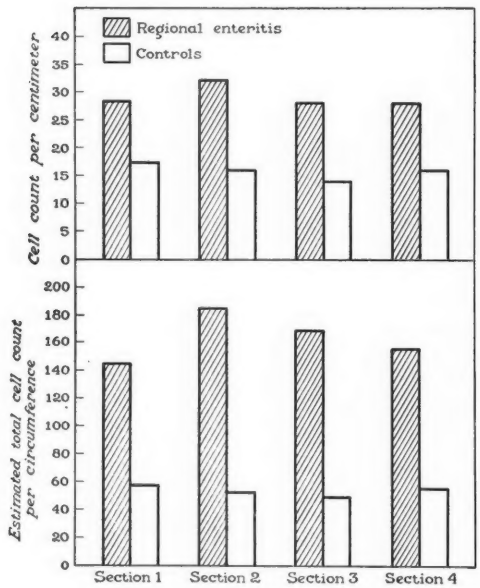


FIG. 2. Actual and estimated total ganglion cell counts from various locations in the ileum.

RESULTS

Some of the clinical and laboratory data, and the average locations of sections cut from the terminal ileum are given in Figure 1 and Table I. The average circumference of the ileum at each location was as follows: in the 24 cases and 24 controls, section 1 was 6.1 and 3.7 centimeters respectively; section 2, 6.4 and 3.9 centimeters; section 3, 7 and 3.9 centimeters; section 4, 6.8 and 4 centimeters. The cell counts and the appearance of the sections and cells are shown in Figures 2 to 8.

In presenting the results of this study, we prefer to answer various questions fundamental, to the study problem and support each answer with corroborating data.

What quantitative difference, if any, exists between the ganglion cells of the myenteric plexus of the ileum of persons suffering from regional enteritis and those of persons not so afflicted? The number of ganglion cells in the myenteric plexus at the ileum in regional enteritis is substantially increased over normal as shown in Figure 2. This was found to be true and fairly uniform in all of the sections studied, including section 4 which was cut orad to the site of disease in normal-appearing bowel in the cases of regional enteritis. The average of all the ganglion cell counts per centimeter for all cases of regional enteritis was 28.89 ± 1.57[1] as compared to 15.71 ± 1.26[1] for the normal controls. The average for estimated total ganglion cells in the circumference, theoretically the most accurate of the two, was 163.5 cells for the regional enteritis group as compared to 53.9 cells for the control series. Thus, it is apparent that persons suffering from regional enteritis possess a complement of ganglion cells in the myenteric plexus of the ileum approximately three times that found in persons not so afflicted.

Do ganglion cell counts vary at different locations in the ileum or are they fairly constant irrespective of where the sample is taken? Inspection of Figures 1 and 2 reveals that the average ganglion cell count per centimeter varied hardly at all between the various sections in

[1]Standard errors of the means.

each group. It is concluded, therefore, that the distribution of ganglion cells throughout the ileum is uniform and counts of ganglion cells at any one location are representative for any other location in a given individual.

Do variations of intestinal circumference reflect a corresponding variation in ganglion cell counts? Averages of circumferences of the ileum and ganglion cell counts per centimeter varied little among the four sections in each group (Fig. 2) and, consequently, no definite conclusion is advanced concerning the influence of intestinal circumference on ganglion cell counts. The average intestinal circumference in the cases of regional enteritis was approximately double that of the controls, yet the ganglion cell counts per centimeter were also approximately twice those of the controls. Any increase in the diameter of the ileum caused by dilatation, as might occur with partial intestinal obstruction, should serve to disperse ganglion cells and thus diminish the number of ganglion cells per centimeter. The fact that counts were increased in the face of such a situation lends support to the hypothesis that the change is absolute rather than relative.

What difference, if any, prevails in ganglion cell counts from persons afflicted with regional enteritis early in life as compared to those afflicted at an older age? The age of the patients in our group with regional enteritis ranged from 13 to 68 years; the average was 33.2 years. The entire group was divided by the mean age and compared as shown in Table II. Ganglion cell counts on patients with regional enteritis operated upon before the average age of 33.2 years were considerably lower than on those operated upon after that age. None of the patients were exactly that age. No satisfactory explanation for this finding is available. If it is assumed that the increase in the number of ganglion cells in the myenteric plexus of the ileum in regional enteritis, or ganglionocytosis to coin a word, is on a congenital level, then the younger patients should exhibit ganglion cell counts equivalent to those of the older patients. Such, however, was not the case.

TABLE I.—CLINICAL AND LABORATORY FINDINGS IN 24 CASES OF REGIONAL ENTERITIS AND IN 24 CONTROLS

		Regional enteritis	*Controls*
Age, yr.	Average	33.2	62.2
	Range	13–68	5–89
Sex	Males	10	13
	Females	14	11
Source of material	Necropsy	—	24
	Operation	24	—
Duration of symptoms	Average	4.6 yrs.	—
	Range	2 wks–17 yrs.	—
Type of disease	Localized enteritis	16	—
	Segmental enteritis	8	—
	Fistula	4	—
	Obstruction	15	—
	Abscess	4	—
	Subacute peritonitis	1	—
Length of involvement, cm.	Average	32.7	—
	Range	8–106	—

Do ganglion cell counts differ in the two sexes? Counts of ganglion cells were slightly higher on females than on males (Table II); however, the slight difference which prevails is scarcely significant.

Does the duration of disease have any influence on the number of ganglion cells in the ileum in regional enteritis? The duration of disease ranged from 2 weeks to 17 years and the average was 4.6 years. The cell counts of 16 patients whose disease had been present less than the mean duration were compared with those of 8 patients with a duration of disease of more

TABLE II.—AVERAGE COUNTS OF GANGLION CELLS IN REGIONAL ENTERITIS AS RELATED TO AGE, SEX, DURATION AND TYPE OF DISEASE, LENGTH OF INTESTINE INVOLVED

		Ganglion cells	
	Patients	*Per cm.*	*Per circumference (estimated)*
Age			
Less than 33.2 yrs.	12	27.5	155.1
More than 33.2 yrs.	12	30.4	171.9
Males	10	26.8	158.3
Females	14	29.0	167.1
Duration			
Less than 4.6 yrs.	16	27.3	152.0
More than 4.6 yrs.	8	32.1	186.6
Partial obstruction	15	27.6	167.1
No obstruction	9	32.2	172.0
Length of intestine involved			
Less than 32.7 cm.	16	28.6	156.6
More than 32.7 cm.	8	29.6	163.4
Segmental disease	—	29.3	169.6
Localized disease	—	28.3	151.3
Controls	—	15.7	53.9

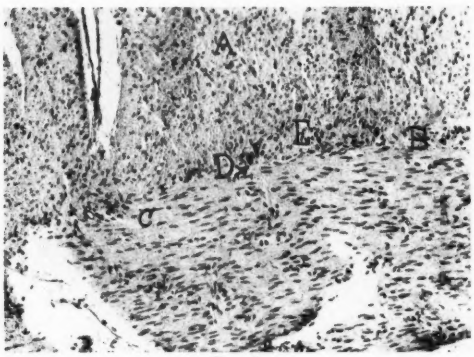


FIG. 3.

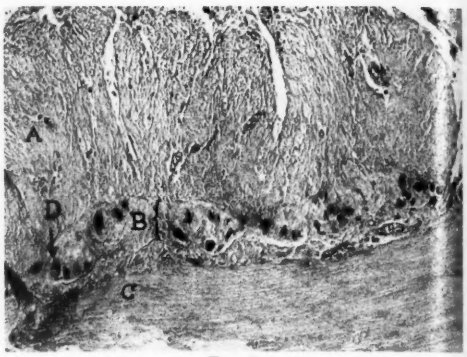


FIG. 5.

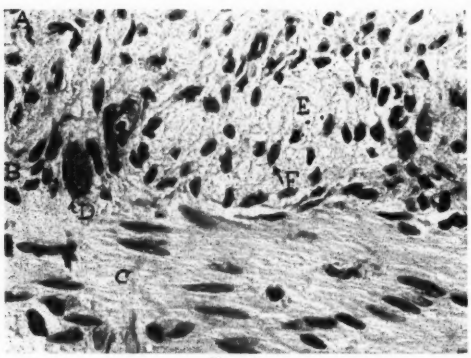


FIG. 4.

FIG. 6.

FIG. 3. Transverse section of terminal ileum from a normal individual; *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, fiber bundle. Cresyl violet, ×75.

FIG. 4. Transverse section of terminal ileum from a normal individual: *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, fiber bundle; *F*, supportive cell. Cresyl violet, ×295.

FIG. 5. Transverse section of terminal ileum in regional enteritis: *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, fiber bundle. The hyperplastic appearance of myenteric plexus in general and the marked increase in ganglion cells as compared to Figures 1 and 2 should be noted. Cresyl violet, ×75.

FIG. 6. Transverse section of terminal ileum in regional enteritis: *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, supportive cell. The marked affinity of the ganglion cells for the stain should be noted. Cresyl violet, ×295.

than 4.6 years (Table II). Persons with longstanding regional enteritis have significantly higher ganglion cell counts than those undergoing operation early in their disease. This finding, supported by the fact that older persons with regional enteritis showed more ganglion cells than young persons, suggests that the increase in ganglion cells is concomitant with the disease and becomes greater as the disease continues. The increase in ganglion cells, therefore, probably is acquired in regional enteritis rather than stemming from some developmental mix-up. Storsteen, Kernohan, and Bargen have postulated that in chronic ulcerative colitis the stimulus of ulceration and increased function may cause small, underdeveloped nerve cells to enlarge and become adult in appearance and function. Our findings in regional enteritis lend support to that theory.

Does the presence of partial intestinal obstruction in regional enteritis have any influence on the number of ganglion cells? The counts of ganglion cells in cases of regional enteritis with partial in-

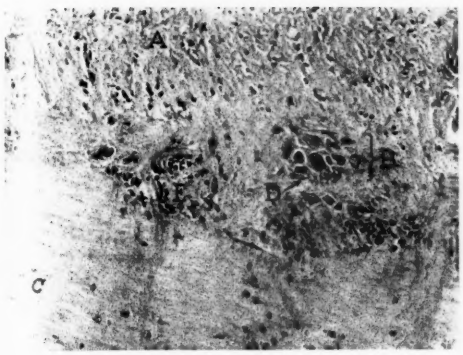


FIG. 7. Transverse section of terminal ileum in regional enteritis: *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, cluster of inflammatory cells. Myenteric plexus is seen to be distorted by inflammation and fibrosis. Cresyl violet, ×75.

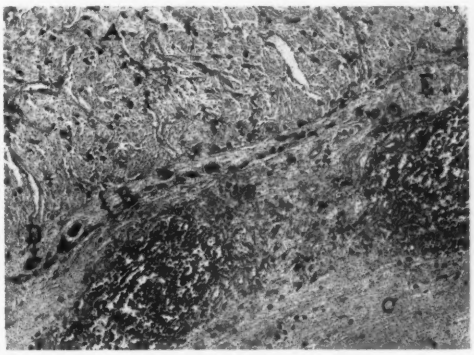


FIG. 8. Transverse section of terminal ileum in regional enteritis: *A*, outer longitudinal muscle; *B*, myenteric plexus; *C*, inner circular muscle; *D*, ganglion cell; *E*, fiber bundle. Ganglionocytosis may be noted in a well-preserved myenteric plexus immediately adjacent to acute inflammation. Cresyl violet, ×75.

tional obstruction were approximately equal to counts made in cases without any obstruction at all (Table II).

Does the extent to which the ileum is involved with regional enteritis have any influence on ganglion cell counts? Gross involvement of the ileum by regional enteritis ranged from 8 to 106 centimeters with a mean of 32.7 centimeters. By comparing ganglion cell counts in cases in which the extent of the involvement was on either side of the mean (Table II), it is evident that the length of ileum involved with disease had no influence on the number of ganglion cells in the myenteric plexus.

Does the presence or absence of segmental disease have any influence on the degree of ganglionocytosis in regional enteritis? Comparison of the ganglion cell counts in 16 cases of localized regional enteritis and in 8 cases of segmental involvement revealed that they were approximately the same in both groups (Table II). The estimated number of ganglion cells in the circumference was slightly greater in the cases of segmental disease but it is questionable whether the discrepancy is sufficient to warrant definite conclusions.

What difference, if any, exists in ganglion cell counts from grossly involved portions of ileum as compared to regions appearing grossly normal? Reference to Figure 2 reveals that ganglion cell counts from areas of disease (sections 1, 2, and 3) were approximately the same as those from regions free of disease (section 4). The fact that the degree of ganglionocytosis in areas of gross disease was equal to that in areas in the same case completely free of gross evidence of disease lends support to the hypothesis that linear shortening of the intestine had a minimal influence on ganglion cell counts obtained by the methods employed in this study.

SUMMARY AND CONCLUSIONS

The number of ganglion cells in the myenteric plexus of the ileum was studied in 24 cases of regional enteritis and in an equal number of controls. Persons suffering from regional enteritis possess in the myenteric plexuses of the small intestine approximately three times as many ganglion cells as persons not so afflicted. Allowances having been made for dilatation, thickening, and shrinkage, the increase seems absolute rather than relative. No satisfactory explanation for this phenomenon is available.

The increase in the number of ganglion cells observed in regional enteritis is not confined to grossly involved portions of small intestine but is present in adjacent normal-appearing bowel as well.

The number of ganglion cells in persons coming to surgery for regional enteritis early in life is significantly lower than that of persons coming to surgery later. Furthermore, regional enteritis of long duration is attended by a greater increase in ganglion cell counts than disease of short duration. These findings support the theory that hypertrophy occurs in small, underdeveloped nerve cells which enlarge to become adult in appearance and function.

Little or no discrepancy exists between males and females with regard to ganglion cell counts in the myenteric plexus, nor does any influence appear to be exerted on counts by the extent of involvement, the presence or absence of intestinal obstruction, or the presence of segmental disease.

The distribution of ganglion cells throughout the ileum is uniform and counts taken at one location are representative of counts at another location in a given individual. Intestinal circumference influences ganglion cell counts in the myenteric plexus only by virtue of condensation or dispersion as might occur with dilatation or circumferential contracture.

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THYROID CARCINOMA IN CHILDREN

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CARCINOMA OF THE THYROID GLAND in children is so uncommon that few physicians have treated more than a single patient with this disease. As a result, the opinions concerning childhood thyroid carcinoma have been based on impressions gained from observations of single or small groups of cases. The largest series were those reported by Joll, Pemberton and Black, Daily and Lindsay, and Duffy and Fitzgerald. These series comprised 43 patients, only 4 of whom were followed for more than 5 years. Only Hare and Salzman and Ward have followed such cases for long periods. Because of the infrequent occurrence of the disease there has been no opportunity to follow a group of patients large enough to be of statistical significance.

A study of thyroid carcinoma in children was begun in 1948 which included only patients in whom a histologic diagnosis had been established prior to the age of 15 years. A preliminary report in 1951 (30) showed that 97 such cases had been reported. Since then it has been found that 7 published cases were overlooked. By means of a survey in the United States 95 unreported cases were found, so data from 199 cases of childhood thyroid carcinoma were available for study. In 1951 a similar study was conducted throughout Western Europe (32). Though 13 countries were visited, only 42 cases were found, 22 of which had been published.

The study of thyroid carcinoma in children has continued with an attempt to obtain tissue slides and the pertinent data on every case reported or found in the surveys. In addition to this, a questionnaire was sent to every children's hospital and to all the large hospitals in Canada and 6 cases were found. Thirty-two new cases were located, 3 of which appeared in Washington, D. C.

A continuing review of the literature on thyroid diseases revealed that 34 additional cases of childhood thyroid carcinoma have been reported since our last publication. In 1951 Horn and Ravdin reported a series of patients with thyroid carcinoma, 3 of whom were less than 15 years of age. Shofner described 1 child with this disease and mentioned another. Seven cases were reported in 1952, 1 each by Barrington-Ward, and Miles and Harsha, and 2 by Lawler, West, and Lawler. Kearns and Davis published data on 3 patients, 1 of whom had been included in our first survey. In 1953 Meckstroth and Curtis described a young girl who was living for 3 years despite widespread metastases. Suárez, Sanz, Velasco, and Peña published data on a 4 year old girl, apparently the first case of childhood thyroid carcinoma from Spain. Seven patients in the series published by Warren, Alvizouri, and Colcock were less than 15 years old, and 3 had been followed for more than 10 years. It was assumed that the cases previously reported from the Lahey Clinic were included in this group. In 1954 Jacobsson described a patient who survived 23 years with proved thyroid carcinoma. In the same year Webster and Howard reported 3 cases from Australia, and Tawast described the only known case of childhood thyroid carcinoma in Finland. The diagnosis of thyroid carcinoma was established before the age of 15 in 8 patients reported by Simpson, Hemplemann, and Fuller.

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TABLE I.—PREVALENCE OF CARCINOMA IN NODULAR GOITERS IN CHILDREN

Source	*Nontoxic nodular goiter*	*Carcinoma*	*Percentage of carcinoma*
Kennedy, R. L. J.	62	12	19.3
Ward, Robertson	10	4	40.0
Hendrick, J. W.	31	8	25.9
Ochsner, Alton	15	4	26.6
University of California	19	10	52.6
Winship, Theodore	8	4	50.0
Total	145	42	29.0

Attitudes regarding thyroid carcinoma have been altered considerably during the last 3 decades. The character of this change was noted recently while studying the large series of cases at the Cleveland Clinic (3). A large proportion of the material examined by Graham 25 years ago consisted of the highly malignant undifferentiated cancers while the slow-growing thyroid cancers were rare. Presumably, cervical lymph nodes enlarged by metastatic carcinoma were often regarded as tuberculous and biopsies were not obtained. Hazard, the present pathologist at the Cleveland Clinic now finds that the majority of the thyroid cancers removed are the slow-growing type.

The diagnosis of thyroid carcinoma in children is being made with increasing frequency. Only 1 case report could be found in the nineteenth century literature. In the first decade of the twentieth century 1 case was reported; in the second decade there were reports of 4 cases; during the next 10 years there were 5 case reports; from 1931 through 1940, 15 authors recorded a total of 40 new cases; during the period from 1941 through 1950, 51 cases were reported; since 1950, 36 cases have been added.[1] Thus, a total of 138 cases of childhood thyroid carcinoma have been found in the European and American literature. One hundred and eight of these were reported from the United States and the remainder from Western Europe and Australia.

The surveys have resulted in the discovery of 23 new cases in Western Europe, 6 in Canada, and 118 in the United States, making a total of 147 unpublished cases. These with the 138 published cases total 285 known cases of childhood thyroid carcinoma.

[1]The cases recorded by Coffee, Amoroso, and Mazzaro are not included because they were reported elsewhere in detail (30).

CLINICAL FINDINGS

All the pertinent clinical information was not available in some instances, hence, the data presented were sometimes based on less than the total number of cases studied.

The sex of most of the children was reported and 64.8 per cent of them were females. This is approximately the same as the accepted figures in adults. Tabulation of the age at which a histologic diagnosis was made in each case ranged from 4 weeks after birth to 14½ years, the average being 9.8 years. The elapsed time between the appearance of the initial symptoms and the establishment of the diagnosis was extremely variable. In only 6 instances was the period less than 1 month and the longest was 11 years with an average of slightly over 2 years. The average patient in this series had a nodule in the neck at the age of 7 years. If the growth rate is uniform it is apparent that thyroid carcinoma may begin at an early age, in fact, 5 children in this series had a thyroid tumor at birth. A mass in the neck had existed since birth in 7 of the cases reported by Warren and associates. Sixty-four per cent of the patients in this series had cervical lymph node metastases when first treated and in 18 per cent of these the metastases were bilateral. Fifteen per cent of the children had pulmonary metastases when first examined and 8 patients had osseous metastases.

It was not possible from the data gathered on children to determine exactly how many malignant tumors arose in nodular goiters. Table I shows the prevalence rate in a small group of cases collected in 1951 (30).

According to these data 29 per cent of 145 nodular goiters in children proved to be carcinoma. This is substantially higher than corresponding figures for adults, but Daily and Lindsay found 59 per cent of the nodular goiters to be malignant in patients less than 20 years old. Only 2 patients in this

series had any symptoms of hyperthyroidism.

Following the report of Duffy and Fitzgerald an attempt was made to determine how many patients in this series had been treated by radiation for an enlarged thymus gland. Only 116 replies were received regarding this inquiry, and 16 patients were stated to have been so treated. This is a considerably higher prevalence rate of thyroid carcinoma than would be expected in a group of nonradiated children. The startling data gathered by Simpson, Hemplemann, and Fuller suggest a causal relation. In their collected group of 1,400 patients treated by radiation during infancy for enlarged thymus, 17 subsequently developed malignant diseases. Six of these patients had thyroid carcinoma.

PATHOLOGY

In order to determine any histologic differences between thyroid carcinoma in children and adults, 2 series of cases were studied. Tissue slides on 130 cases of childhood thyroid carcinoma were available. Through the courtesy of certain physicians in several large clinics, it has been possible during the past 2 years to study large numbers of cases of thyroid carcinoma. These, with our own material, comprised 596 cases of adult thyroid carcinoma. The 2 groups of cases were classified by using the same criteria. The results are shown in Table II.

TABLE II.—PATHOLOGIC TYPES OF CHILDHOOD AND ADULT THYROID CARCINOMA

	Adults		*Children*	
Cell type	*No.*	*Per cent*	*No.*	*Per cent*
Papillary adenocarcinoma	89	15	21	16
Papillary and follicular adenocarcinoma	184	31	41	31
Follicular and papillary adenocarcinoma (cases showing a papillary element)	89 (61)	15	23	18 (65)
Follicular adenocarcinoma	102	17	26	20
Oxyphilic (Hürthle cell) adenocarcinoma	18	3	0	0
Undifferentiated adenocarcinoma	107	18	19	15
Lymphoma	7	1	0	0
Total	596	100	130	100

The classification used is similar to that of Warren and Meissner (28) but has been somewhat simplified for the use of students (31). It is practical for routine use and the terms are descriptive. Prognosis is based upon the clinical stage of the disease and the predominate cell type so the tumors are arranged in the order of increasing malignancy. Compound terms are used because the majority of cancers are composed of 2 cell types. When multiple sections of a tumor are studied 3 or even 4 distinct cell types may occasionally be identified. Eponymic terms are not used for they do not have the same meaning to all pathologists. Since radioiodine is utilized only by functioning follicles, their presence is indicated by adding the adjective "follicular" to the diagnosis. The term alveolus is not used since by histologic definition alveoli are not found in the thyroid gland. The words medullary and scirrhous describe gross findings but have no microscopic or clinical significance. All cancers of the thyroid gland, except the very rare squamous carcinoma, are considered to be adenocarcinomas so the use of this term to describe a single type would be confusing.

The diagnosis of thyroid carcinoma is established in the same way as in other types of carcinoma. The decision is made after an evaluation of the structure of the tumor, the degree of anaplasia, the number and nature of mitoses, and the presence of invasion. Blood vessel invasion, when proved by special stains is of value but it should not be the sole basis for the diagnosis of carcinoma. Calcospherites (psammoma bodies) are sometimes helpful in making a diagnosis of thyroid cancer. These are most often present in tumors having a papillary element but they may be found in any type of benign or malignant goiter, or in lymph nodes containing metastatic thyroid carcinoma.

Though 61 per cent of the 726 cases in this study showed a papillary element only 15 per cent of the cases were purely papillary in pattern. A variety of types of papillary carcinoma were seen but the most common type is shown in Figure 1. Since no follicles were present in the pure papillary carcinomas, these tumors had no affinity for

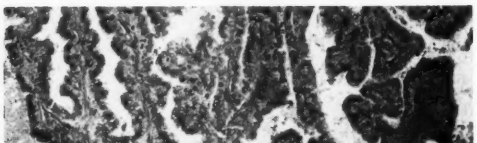

FIG. 1. One type of pure papillary adenocarcinoma.

radioiodine. The papillary and follicular tumors were characterized by a predominantly papillary pattern with scattered single or groups of follicles, many of which contained colloid (Fig. 2). The term follicular and papillary adenocarcinoma described tumors composed chiefly of malignant follicles but with foci of papillary carcinoma (Fig. 3). The follicular category (Fig. 4) consisted of tumors composed only of follicles. The follicles were often well differentiated and the tumors appeared to be of relatively low grade malignancy. Some of these, however, were composed of poorly formed follicles without colloid and were lined by characteristic cancer cells. The carcinomas variously called malignant adenomas, carcinomas arising in adenomas, microfollicular carcinomas or malignant fetal adenomas were included with the follicular group since most of them developed follicles of some type. The tumor composed of large oxyphilic cells, called Hürthle cell carcinoma in the United States has been reported only once in a child. So far as can be determined lymphoma of the thyroid gland has not been reported in children.

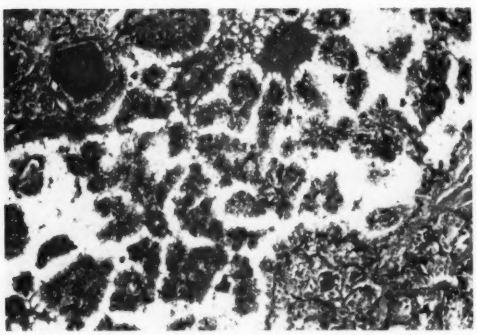

FIG. 2. Papillary and follicular adenocarcinoma. These tumors are predominantly papillary in structure but have a few colloid containing follicles.

Included in the category of undifferentiated carcinoma were the solid carcinomas, the spindle and giant cell carcinomas, the so-called small cell carcinomas and other unclassified tumors (Figs. 5, 6, and 7). Most of these cancers were highly malignant but occasionally patients with tumors of this type lived for long periods. The high percentage of undifferentiated cases in children may be explained by the large number of such cases in the European group. Twenty-two per cent of these cases were classified as undifferentiated carcinoma, whereas, only 10 per cent of the United States and Canadian cases were so classified. This geographic difference is probably only apparent and may have occurred because European pathologists did not consider many of the papillary tumors to be malignant.

Despite impressions gained in the past, the pathology of thyroid carcinoma in children and adults is very similar. The percentage of each type of tumor is nearly the same. Any type of thyroid carcinoma may metastasize to cervical lymph nodes, and from there it may erode into veins and produce further metastases. Any type may invade the muscles of the neck, though this rarely occurs in papillary carcinoma. One difference between papillary carcinoma in children and adults was the size of the tumor. Frazell and Foote found in a series composed chiefly of young adults that 15 per cent of the papillary tumors measured less than 1 centimeter. In this series only 3 per cent of the papillary tumors measured less than 1 centimeter and in most cases at least the major portion of the lobe was involved.

GEOGRAPHIC DISTRIBUTION

It has often been stated that the prevalence of thyroid carcinoma is greatest in

goitrous regions. Such impressions have been gained from the preponderance of reports from investigators in the goitrous areas in which interest in thyroids was high. In a complete survey of Finland, Saxén did not find any greater prevalence of thyroid carcinoma in the goitrous areas than in the nongoitrous regions. Endemic goiter has been markedly reduced in the canton of Bern, Switzerland, by the use of iodized salt. However, Thalmann found that the prevalence of thyroid carcinoma in that area had not changed in the past 40 years. The distribution of cases in this study of childhood thyroid carcinoma was widespread, but no greater prevalence of thyroid carcinoma was found in the goitrous regions than in the nongoitrous areas. The greatest number of cases occurred in the areas of greatest population concentration and in the location of the large medical centers (Figs. 8 and 9). This was true with certain exceptions. Thyroid carcinoma was found with relative frequency in certain centers, whereas, in nearby cities of greater size and with equal medical facilities, none was found. It appears that the prevalence of thyroid carcinoma in any single region is more closely related to the interest in the disease than to the geographic nature of the region.

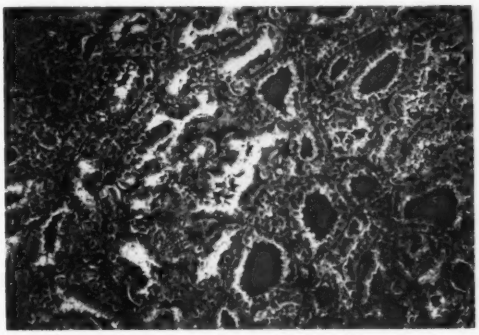

FIG. 3. Follicular and papillary adenocarcinoma, predominantly follicular, but with small foci of papillary carcinoma.

THERAPY

Treatment was so varied that comparisons were difficult, and lack of adequate follow-up examinations made evaluation of therapeutic methods of limited value. A satisfactory evaluation of the various surgical methods was difficult because of confusion in surgical terminology. It was impossible to determine the amount or location of thyroid tissue remaining after a procedure variously described as an excision, a subtotal lobectomy, a lobectomy, or a hemithyroidectomy. The interpretation placed upon the terms total thyroidectomy and subtotal thyroidectomy was equally variable.

In 92 per cent of the children an attempt was made to eradicate the tumor surgically. In the others a lesser procedure was chosen. A total or subtotal thyroidectomy was performed in 39 per cent of the patients and a lobectomy only in 21 per cent. In 30 per cent of the patients a radical neck dissection was performed and in 11 patients the procedure was bilateral. Thirty per cent of the surgically treated patients had additional surgery consisting of 1 or more operations to remove a recurrent or residual tumor in the neck. These operations followed the original surgery by variable periods averaging 4½ years. In 1 of the cases submitted by Penner the original operation was performed in 1926 for an "aberrant thyroid." Twenty-six years later a radical neck dissection was discontinued because the condition was considered to be inoperable. The tumor was a

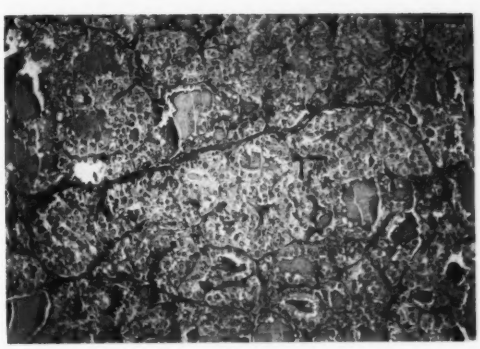

FIG. 4. Follicular adenocarcinoma. Some of the follicles are functional, but others are not producing colloid and some do not have a lumen.

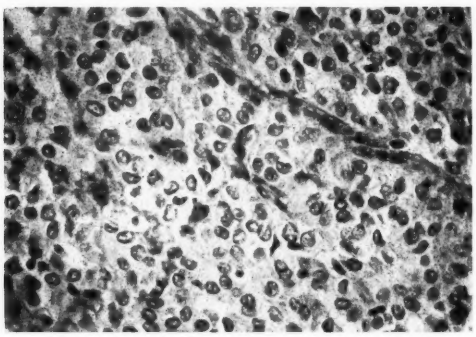

FIG. 5. Undifferentiated adenocarcinoma, solid type, composed of closely packed large cells.

follicular carcinoma so the patient is now being treated with radioiodine. A patient described by Trevor and Pack was first operated upon at the age of 12 years. One year later a nodule of metastatic thyroid carcinoma was removed from her choroid plexus. She is now living without evidence of disease 19 years after the craniotomy. Methods of surgical therapy could be roughly divided into the conservative, intermediate, and radical categories. Some surgeons removed only the grossly involved thyroid tumor. Others performed a lobectomy and excised the grossly involved lymph nodes. The radical operation consisted of a total thyroidectomy and a radical neck dissection on the involved side. The best methods of therapy could not be determined because no large group of patients treated in the same manner has been adequately followed at this time. It can only be stated that as much of the tumor as possible should be resected surgically regardless of the type of carcinoma.

Only 42 per cent of the children received x-ray therapy and 18 per cent received therapeutic amounts of radioiodine. The pulmonary lesions in 3 patients were reported to have disappeared following the use of radioiodine. Five patients in this series were treated in part by radium. All except 1 of these children were treated in Europe. The value of x-ray therapy has not yet been determined for only a few cases treated solely by this method have been followed for as long as 10 years.

RESULTS

Follow-up data were available on 192 patients. Many of the children have been followed for only a few years so were not included in these statistics. Forty-eight have been followed for over 5 years, 17 for 10 years, 10 for 15 years, and 10 for 20 years. In the group followed for more than 10 years 30 patients are apparently free of disease and 5 are known to be living with disease, 1 patient for over 27 years. One patient died of her disease 23 years after the first operation. Seventy-four per cent of the patients living

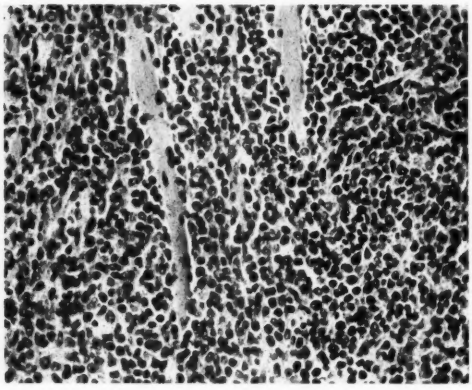

FIG. 6. Undifferentiated adenocarcinoma composed of small cells involving the sternomastoid muscle.

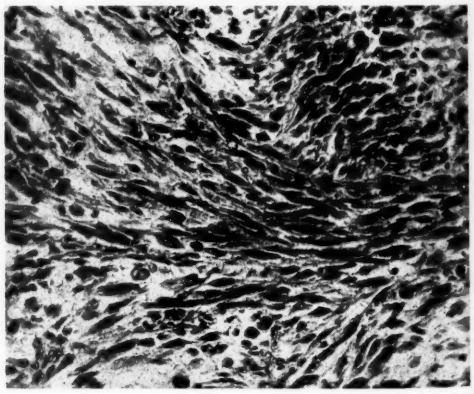

FIG. 7. Undifferentiated adenocarcinoma, spindle cell variety.

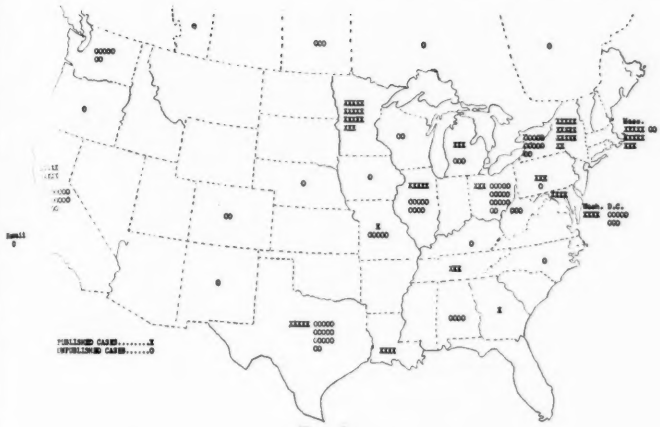

FIG. 8.

FIG. 8. Distribution of the known cases of childhood thyroid carcinoma in the United States and Canada.

FIG. 9.

FIG. 9. Distribution of the known cases of childhood thyroid carcinoma in Western Europe.

for more than 10 years had tumors containing a papillary element, 18 per cent had pure follicular carcinoma, and 8 per cent had undifferentiated carcinoma.

The prognosis for children with thyroid carcinoma is not good. Forty-eight or 16.7 per cent of the entire series died of their disease. Nine of them died shortly after operation and the others after variable periods of time up to 23 years. Sixty-five per cent of the deaths were caused by tumors containing a papillary element, 22 per cent by follicular carcinoma, and 13 per cent by undifferentiated carcinoma. These results should emphasize the importance of prompt and adequate therapy for children with thyroid carcinoma regardless of the cell type.

In view of the recurrences after long periods of quiescence it is apparent that a follow-up study of less than 20 years in patients with thyroid carcinoma is of relatively little value. Only in children would this be possible since adults too often die of unrelated diseases before a 20 year follow-up is completed. The results of this study corroborate the work of Lees and Park, Klopp, and others in disproving the impression that carcinoma grows more rapidly in children than in adults. It is hoped that this study can be continued long enough to determine the outcome of a group large enough to be of statistical significance.

SUMMARY

The literature relative to childhood thyroid carcinoma is reviewed. To date 138 cases of this disease have been reported.

An additional 147 unpublished cases were located by surveys conducted in the United States, Canada, and Western Europe. Thus, data from 285 cases of childhood thyroid carcinoma were available for study.

The clinical, pathologic, and geographic aspects of carcinoma of the thyroid in children are reviewed.

A review of the literature gave the impression that thyroid carcinoma was quite a different disease in children than in adults. Analysis of this series, however, does not show any remarkable difference in the clinical manifestations, the histologic types, or the progress of the disease.

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A NEW TECHNIQUE FOR COMPILATION ARTERIAL GRAFTS: VINYON 'N' CLOTH SUPPLEMENTED WITH A LONGITUDINAL AUTOGENOUS ARTERIAL STRIP

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DESPITE THE CURRENT POPULARITY of arterial homografts for clinical use, experimental observations in our laboratory indicate that their long term results may not always be as satisfactory as might be desired. This question is particularly significant when homografts are implanted in children or young adults. The present article concerns the experimental study of another type of graft which we hope may obviate certain of the objections to arterial homografts.

UNDESIRABLE FEATURES OF HOMOGRAFTS

Homografts manifest essentially two undesirable features. First, they do not keep pace with the growth of the host aorta when inserted in a growing animal. Second, they frequently develop marked degenerative changes. These so-called degenerative changes consist of calcification within the wall of the graft, subintimal plaques and hemorrhages, cracking of the intima, and mural thrombi. The grafts usually become rigid, thick tubes smaller than the host aorta. These changes are moderate in some grafts, but severe in others. Unfortunately, we are unable to predict the outcome of a given graft in a given animal. However, despite this undesirable situation, homografts are usually successful carriers of blood. On this fact is based their so far successful clinical application.

What remains unknown is how long a homograft will endure as an effective carrier of blood. Will these degenerative changes eventually result in a high incidence of thrombosis, embolism, stenosis, or aneurysm? Will failure of the graft to grow with the host aorta result in a deleterious constriction of the aorta after full growth is attained? The answers may not come from the laboratory because experimental animals do not live long enough. Of great interest, therefore, will be the long term results of homografts inserted in children following resection of aortic coarctation. Gross has followed 16 of these cases for 4 years with good clinical results. However, 3 of the 16 homografts show calcification by x-ray examination. These 3 grafts, therefore, have most probably undergone severe degenerative changes. Furthermore, we have observed severe degenerative changes in experimental homografts which show no calcification by x-ray examination. Therefore, Gross' remaining 13 patients may not necessarily be free of degenerative changes merely because calcification is not seen in the x-ray picture.

Thus, there is good evidence that the results of homografts in the human are similar to the results of homografts in the experimental animal. These results leave room for improvement, namely, that the graft grow and be free of degenerative changes.

CURRENT APPROACHES TO THE PROBLEM

Autogenous tissue. The results of autogenous arterial grafts are excellent, but their availability is so limited that clinical application

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is restricted. Schmitz and associates reported a clever method for compiling the subclavian artery into a graft suitable for insertion in the aorta, but again the available amount of subclavian artery restricts its use for bridging only short aortic defects.

With the idea that other autogenous tissue will grow and not develop degenerative changes, we have tried inferior vena caval and pericardial autografts in the thoracic aorta. These all tend to dilate or develop aneurysms and some have ruptured. Supporting these grafts with diaphragmatic tendon or wrapping them with viable intercostal muscle pedicles does not prevent these complications. The application of sclerosing agents such as dicetyl phosphate and latex diminishes the frequency and severity of dilatation and aneurysm formation, but not completely or consistently. Their clinical use is, therefore, hazardous and not recommended.

Arterial homografts. The reasons for the development of degenerative changes in homografts are unknown. Immune factors between host and donor are considered important. If these factors could be modified, it is conceivable that degenerative changes could be eliminated. It is further conceivable that in the absence of degenerative changes, the host tissue replacing the graft could grow and result in a graft similar to the host aorta. Toward this end we are treating homografts with various chemical agents, which may not only be effective in sterilizing and preserving the grafts, but may also modify their antigenic properties. This work is in progress and shows promise.

We are also interested in the approach of diminishing or neutralizing antibody production by the host animal with various sera. Such work is in a preliminary stage in our laboratory and may be the key to the whole problem of grafting viable and nonviable homologous tissue. In this regard, the recent report of Good and Varco is most intriguing. A patient with a-gamma globulinemia was successfully grafted with homologous skin.

Flexible plastic cloth. Vinyon 'N' plastic cloth was successfully used to bridge abdominal aortic defects in dogs by Voorhees, Jaretzki, and Blakemore in 1952 and with further experimental success, in 1954 they reported their clinical success in grafting the human aorta with vinyon 'N.' Stimulated by these efforts, various other groups have since reported their experience with other plastic cloths. Shumacker and associates (8, 9) have used pliable grafts of fused nylon and polythene cloth experimentally and clinically. Hufnagel has experimented with vinyon 'N,' nylon, orlon, and dacron. He expressed a preference for orlon, and has used it successfully in the human. D'Angelo and associates have confirmed the original experimental work of Voorhees and coworkers with vinyon 'N.'

This work has concerned the use of plastic cloths in adult animals and man. Since one of our main interests has concerned growth of aortic substitutes, we have investigated the use of vinyon 'N' in the growing animal.

VINYON 'N' IN THE GROWING AORTA

Bridging a defect in a growing aorta with an inert flexible plastic cloth poses several problems. The factor of growth introduces complexities which are not present in the case of the adult aorta. To evaluate the problems concerning growth, grafts have been implanted in weanling pigs and examined at slaughter when full growth is attained. The fact that pigs grow much faster than humans must be considered in interpreting these results. Pigs reach adult size in less than a year.

The proximal descending thoracic aorta has been selected as the site for grafting because this area seems to offer a most rigorous test for any graft. For example, Kanar reported that homografts implanted in the abdominal aorta do not develop degenerative changes as frequently or as severely as homografts in the thoracic aorta. Furthermore, grafts which show a tendency to dilate and rupture, for example, venous autografts, do so more frequently and severely in the

thoracic than in the abdominal aorta. We, therefore, use the proximal descending thoracic aorta to evaluate the occurrence of undesirable changes in arterial grafts.

OPERATIVE PROCEDURE

Technique. Under aseptic precautions, the left chest was entered through the bed of the fifth or sixth resected rib. The proximal descending thoracic aorta (from the obliterated ductus arteriosus distally) was mobilized with ligation and division of the intercostal arteries arising from the portion of aorta to be removed. The aorta was occluded proximally and distally by Potts coarctation clamps, and a suitable segment of intervening aorta was excised. Blood flow was immediately re-established through a polished Teflon shunt secured to the cut ends of the aorta with braided silk ties. The grafts were then sutured in place with No. 5–0 silk. Before completion of the proximal anastomosis, the Potts clamps were reapplied to permit removal of the shunt. The proximal anastomosis was then completed, the clamps removed, and blood flow established through the graft. Measurements were recorded of graft length and diameter, the diameters of both anastomoses, and diameters of the host aorta at measured distances (tagged by sutures) above and below the graft.

Series A.—Fourteen tubes made entirely of vinyon 'N'[1] (without a supplemental strip of aorta) were implanted. The grafts varied in length from 3.0 to 7.5 centimeters, and in diameter from 1.0 to 1.3 centimeters. Each graft was tailored at the time of surgery so that its diameter equalled that of the host aorta. Equal dimensions of graft and aorta facilitated the suturing of anastomoses, and minimized wrinkling and folds of the cloth at the suture lines. Each graft was made of such a length that it was sutured under slight tension. If this tension is absent, the graft is too long, and accordion-like pleats occur as the graft shortens to fit itself between the cut ends of the aorta. The anastomoses were of a continuous over-and-over suture of No. 5-0 silk placed in such a manner that the vinyon 'N' encircled the aorta as a female cuff.

[1]The vinyon 'N' used is 37 denier, 144 by 90 strands per square inch. It was sterilized in boiling water for 20 minutes just prior to insertion.

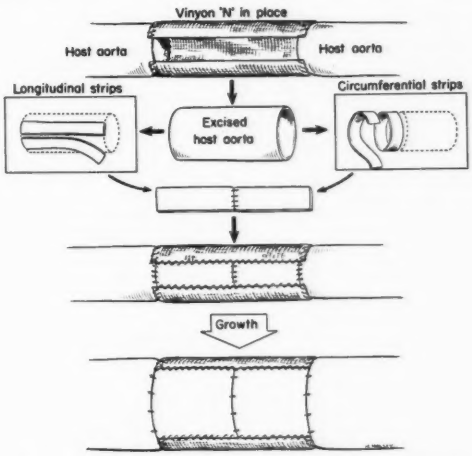

FIG. 1. The top illustration shows the method of suturing vinyon 'N' to aorta. Continuous sutures are placed in such a manner that the cloth encircles the aorta like a female cuff. The graft is supplemented with longitudinal aortic strips.

Series B.—Eighteen grafts of vinyon 'N' with supplemental longitudinal strips of autogenous aorta were inserted. These grafts varied in length from 2.7 to 5.0 centimeters and in diameter from 1.0 to 1.4 centimeters.

The vinyon 'N' portion of the graft was first sutured in place proximally and distally. Strips of aorta were then cut from the previously excised segment of aorta. Some strips were cut longitudinally and others circumferentially from this aortic segment. Two such strips placed end to end were needed to fill in the longitudinal rectangular defect of the graft. Thus, the strips cut from the aortic segment longitudinally were grafted longitudinally, while those cut circumferentially (transversely) were turned 90 degrees to also be grafted longitudinally (Fig. 1). Interrupted No. 5-0 silk sutures (to allow growth) were used to suture the ends of these aortic strips together, and to suture them to the host aorta. These anastomoses were

TABLE I.—14 TUBES OF VINYON 'N' (SERIES A)

Results	*Remarks*
2 failures.....	1. Thrombosed aneurysm of host aorta just distal to graft 2. Thrombosis of graft in midportion. Duration of implantation: 8 and 9 months
2 successful grafts (excluded from study).	Death from unrelated causes. Both grafts patent. Intima smooth. No thrombi. Duration of implantation: each 1 month
10 successful grafts...	All grafts were widely patent. Intima smooth. No thrombi. Eight of the 10 grafts showed various degrees of calcification adjacent to the vinyon 'N.' Seven of the 10 grafts were shortened with pleating of vinyon 'N.' Pleating did not narrow the lumen significantly. Duration of implantation: 6 to 9 months; average 7 months

end-on, and not everted. Continuous over-and-over sutures of No. 5-0 silk approximated the sides of the aortic strips to the vinyon 'N.'

The width of the aortic strips was varied. In 10 grafts the aortic strips varied from 0.8 to 1.2 centimeters wide, and constituted approximately 25 per cent of the graft's total circumference. The remaining 75 per cent consisted of vinyon 'N.' In 6 grafts this ratio was reversed. That is, the aortic strips were wider, and constituted more than half of the total circumference. In 2 pigs the grafts were constructed so that 50 per cent of the graft's circumference was artery and 50 per cent vinyon 'N.'

Initial technical difficulties. Insertion of a plastic cloth graft is technically more tedious and difficult than an arterial or venous graft. Although flexible, the cloth is inelastic and, therefore, cannot be fitted into an arterial defect as easily as an elastic graft of artery, vein, or other tissue. Wrinkling of the cloth at the anastomoses predisposes to thrombosis at the anastomoses, and can be avoided if the ends of the plastic cloth are made the same size as the cut ends of the host aorta. The length of the graft should also be just slightly shorter than the aortic defect. If too short, it can not be stretched to fill this defect, and if too long, it will shorten itself by accordion-like folds which predispose to thrombosis within the graft. After experience with cloth is acquired, the technique is no more difficult than working with arterial homografts.

Different types of sutures to approximate the grafts to the host aorta were first tried. The method shown in Figure 1 was most satisfactory in this study.

Whereas bleeding at anastomoses of artery to artery may usually be controlled by finger tip compression, bleeding at anastomoses of cloth to artery may be more difficult to control. Finger tip compression is a definite aid, but a supplemental stitch is often required.

Most reports on the use of plastic cloth grafts mention that bleeding through the pores of the vinyon 'N' immediately after its insertion is sometimes severe. For unknown reasons, this type of bleeding does not occur through vinyon 'N' implanted in the thoracic aorta of a pig. However, it does occur through vinyon 'N' implanted in the abdominal aorta of a dog, and is especially severe when the graft is lengthy. We are unable to explain our observations that dog blood leaks through vinyon 'N' much more profusely than pig blood. The problem of initial bleeding through the graft wall has been approached by different methods, those of Blakemore, Hufnagel, and Shumacker.

RESULTS

In all but a few instances, the pigs were slaughtered after full growth was attained, approximately 7 months postoperatively. Average weight gain was from 15 kilograms at the time of surgery to 82 kilograms at the time of slaughter. Average gain in crown to rump length was from 59 to 105 centimeters. Each graft was removed with some proximal and distal host aorta attached. These specimens were then distended with air forced under a pressure of 120 millimeters of mercury, and the same measurements taken at the time of surgery were repeated. The grafts were opened longitudinally for examination of their walls and intimal surfaces. Photographs were taken of the grafts in their distended and opened states. The grafts were then sectioned for microscopic study and preserved.

FIG. 2. FIG. 3. FIG. 4.

IG. 2. Result of graft constructed entirely of vinyon ' Specimen distended with air at 120 millimeters of r cury. When inserted at surgery the graft and aorta v isodimensional. The diameter of the aorta almost d bled by growth. The graft represents a constricted s ent in the aorta and in this respect resembles many o ar homografts. Note that the graft is covered with fi us tissue.

IG. 3. The intimal surface of the graft in Figure 2 o ned longitudinally. The vinyon 'N' is covered by l ous tissue with a smooth endothelial lining.

FIG. 4. Another graft constructed entirely of vinyon 'N' in the opened state. The pliable aorta is unrolled to lie relatively flat, but the more rigid graft can be only partially unrolled. Note the pleating of the vinyon 'N,' which is the most marked in this series. However, the intimal surface is unwrinkled, smooth, and glistening. This graft was 6.7 centimeters long when inserted, and in the distended state after slaughter was 6.0 centimeters long. In this opened state the graft has recoiled to 5.5 centimeters. It also represents a constriction in the adult aorta.

Series A. Fourteen tubes made entirely of vinyon 'N' (Table I).—Two of the 14 grafts are considered failures. One of these failures showed complete old thrombosis in only the midportion of the graft. The graft was inserted early in this series before full technical competence was attained, and the proximal anastomosis was slightly constricted. However, both anastomoses and ends of the graft were patent. This complication has not occurred elsewhere in this series and is unexplained. The other failure consisted of a huge thrombosed fusiform aneurysm of the aorta immediately distal to the graft. The entire graft was patent, however. The cause of this aneurysm is uncertain, although this pig's immediate postoperative course was complicated by a large wound abscess and empyema, with recovery in 2 months. Both animals lived 8 months until slaughter with no ill effects other than poor weight gain.

The remaining 12 grafts are considered successful. However, 2 of these 12 animals died 1 month postoperatively. One died of a bowel strangulation, and the other was a "runt" which did not grow and was probably killed by other pigs. At autopsy both grafts were widely patent.

The remaining 10 pigs continued in good health with normal growth until slaughter some 7 months postoperatively. On external examination these grafts resembled the majority of our aortic homografts in that they were firm to rigid, thick-walled, inelastic tubes of smaller diameter than the host aorta (Fig. 2). The diameters of the host aortas adjacent to the grafts grew from 1.0 to 1.3 centimeters, at the time of surgery, to 2.1 to 2.5 centimeters, at the time of slaughter. Thus, the diameters of the host aortas were approximately doubled by growth.

The length of 3 of the 10 grafts remained unchanged (3, 3.8, and 6.5 centimeters; Fig. 3). The length of the other 7 grafts decreased. The amount of decrease in length was not related to the original length of the graft. That is, the longer grafts did not shorten more than the shorter grafts. Thus, one 3 centimeter graft shortened to 2.5 centimeters, and a 7.5 centimeter graft shortened to 6.7 centimeters. The greatest decrease in length occurred in a graft 5.5 centimeters long which shortened to 4.4 centimeters. The least decrease in length occurred in a graft 6.5 centimeters long which shortened to 6.3 centimeters.

Thus, the occurrence and amount of graft shortening appeared haphazardly in this series. We are unable to explain why some grafts shortened and others did not, or why

FIG. 5. Photomicrograph of longitudinal section of vinyon 'N' graft in place for 7 months. The vinyon 'N' occupied the wavy space running along the section. The cloth fibres were separated from this section by the microtome blade during cutting of the block. Note that fibrous tissue encases the vinyon 'N' on both surfaces. The hills and valleys of the pleated cloth are filled with fibrous tissue in such a manner that the intimal surface is smooth. Calcification is not present in this section.

some grafts shortened more than others. The amount of tension on each graft at the time of insertion may explain these differences.

As expected, shortening of the grafts was accompanied by accordion-like pleating of the vinyon 'N.' In no instance did this infolding of the graft occur at one point with buckling of the graft to jeopardize its lumen. Infolding was always accompanied by many small circumferential folds throughout the graft's length which did not diminish the graft lumen significantly. The folds were never more than 1.5 millimeters in height. Furthermore, the valleys in between the hills of the folds were filled in with collagenous tissue so that the intimal surface was always smooth and unwrinkled (Figs. 4 and 5). Shortening of the graft by pleating did not give rise to a wrinkled intimal surface predisposed to thrombosis, nor did it significantly decrease the lumen of the graft.

The immediate and subsequent response of the host to vinyon 'N' seems to be one of tissue repair and healing. In brief, blood first penetrates the cloth and clots within the cloth fibers. This fibrin organizes with the laying down of collagenous tissue. The inner surface is covered by an endothelium which may arise from the host aorta at each end of the graft, or from fibroblasts in a multicentric origin throughout the graft. The end result is a tube lined with smooth endothelium, beneath which is a layer of dense scar. The vinyon 'N' is imbedded in this scar, which is usually 1 to 2 millimeters thick on each side of the cloth (Figs. 5 and 6). In 8 of the 10 grafts, irregular patches of calcification were present immediately adjacent to the vinyon 'N.' Calcium was laid down in a very thin layer. In all instances it was thinner than half the thickness of an egg shell. This calcification did not appear to be as deleterious as that within an aortic homograft. In the latter, calcification is often a thick subintimal plaque which appears to cause intimal ulceration. When calcification occurs in vinyon 'N' grafts it occurs as a very thin layer well beneath the new intima and adjacent to the cloth. The intima is smooth and apparently not affected by this calcification. For unknown reasons, calcification occurred oftenest on the intimal side of vinyon 'N.'

The occurrence of calcification in vinyon 'N' grafts is interesting in that it has not been previously reported. In other studies, vinyon 'N' was placed in the abdominal aortas of mature dogs. In this study, vinyon 'N' was placed in the thoracic aortas of growing pigs. A different animal, especially a growing one, may account for the difference. The fact that more calcification occurs in arterial homografts implanted in the thoracic aorta than in the abdominal aorta may also have some bearing. We have not had enough experience with other plastic cloths to state that this calcification occurs only with vinyon 'N.'

Series B. Eighteen grafts of vinyon 'N' plus autogenous aorta (Table II).—Though all 18 grafts were successful in that they served as functional carriers of blood, 2 grafts are considered failures as regards the objects of this study. One graft was partially surrounded by an organized hematoma (false aneurysm). Blood had evidently escaped through a leak at the proximal anastomosis, at which point an old thrombus partially occluded the graft and proximal host aorta. Except for this complication, which was most probably a result of poor technique, the graft could be classed with the

remaining 16 successful ones. The other failure presented peculiar findings. The autograft portion was calcified, and this calcification extended diffusely into both ends of the host aorta for about 0.4 centimeter. No growth occurred at the proximal anastomosis which was, therefore, a point of constriction, but the graft and distal anastomosis grew the same as the host aorta; that is, the aortic strip grew in width.

Three pigs are excluded from further discussion because they died of unrelated causes approximately 1 month postoperatively. All 3 grafts were patent with smooth intimal surfaces and contained no thrombi or calcification. Growth had not occurred in the 1 month following implantation.

Of the remaining 13 grafts, 6 were those with vinyon 'N' constituting about 75 per cent of the circumference of the graft, 5 with vinyon 'N' approximately 25 per cent of the circumference, and 2 in which the circumference was 50 per cent vinyon 'N' and 50 per cent aortic strips.

The growth of the host aortas in this series was comparable to that in series A. That is,

TABLE II.—EIGHTEEN GRAFTS OF VINYON 'N' PLUS LONGITUDINAL AORTIC STRIPS (SERIES B)

Results	*Remarks*
2 failures (but functionally successful).....	1. False aneurysm (leak at proximal anastomosis) 2. Calcification of autogenous aortic portion of graft and adjacent host aorta. No growth of proximal anastomosis. Duration of implantation: 8 and 9 months
3 successful grafts excluded from study	Death from unrelated causes. All 3 grafts patent. Intima smooth. No thrombi. Duration of implantation: each 1 month
*6 successful grafts (vinyon 'N' 75 per cent of original circumference)...	Increase in width of aortic strips from 25 per cent of original graft circumference to 50 per cent of adult graft circumference. Grafts straight and isodimensional
*2 successful grafts (vinyon 'N' 50 per cent of original circumference)...	Increase in width of aortic strips from 50 per cent to 70 per cent of adult graft circumference. Grafts slightly bowed and isodimensional
*5 successful grafts (vinyon 'N' 25 per cent of original circumference)...	Increase in width of aortic strips from 75 per cent to 85 per cent of adult graft circumference. Grafts moderately bowed and isodimensional

*Aortic strips retained original characteristics and grew.
Five of the 13 grafts showed calcification adjacent to vinyon 'N' portion. Four of the 13 grafts showed some pleating of vinyon 'N.' All 13 grafts showed smooth intima with no thrombi.
Duration of implantation: 6–9 months; average 7 months.

FIG. 6. Anastomosis of vinyon 'N' (right) to autogenous aorta (left) after 7 months. The intimal surface is smooth throughout, and the union is strong.

their diameters were approximately doubled. In all instances, the autogenous aortic graft strips retained their original appearance, and at slaughter resembled the host aorta in all respects. Furthermore, these aortic strips grew in width so that the grafts and anastomoses grew with the aorta. At slaughter, the lumens of the grafts approximated the lumens of the aortas, and the grafts, anastomoses, and adjacent aortas were almost isodimensional.

The narrow aortic strips, comprising about 25 per cent of the graft circumference, grew almost 3 times their original width so that after full growth they comprised 40 to 50 per cent of the total circumference of the graft (Figs. 7 and 8). The wide aortic strips, comprising about 75 per cent of the graft circumference, grew 1½ to 2 times their original width, so that after full growth they comprised, on the average, 85 per cent of the graft circumference (Figs. 9 and 10). The same growth in width occurred regardless of whether the aortic strips (all inserted longitudinally in the graft) were taken longitudinally or circumferentially (transversely) from the segment of aorta excised at surgery.

These aortic strips also grew in length. This lengthwise growth was variable. It ranged from a minimum of 0.2 centimeter in one graft 3.8 centimeters long, to a maximum of 1.2 centimeters in a graft 4.4 centimeters long. Lengthwise growth of the arterial portion of the graft resulted in bowing of the graft. The shorter vinyon 'N' portion

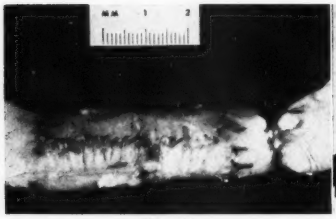

FIG. 7.

FIG. 8.

FIG. 9.

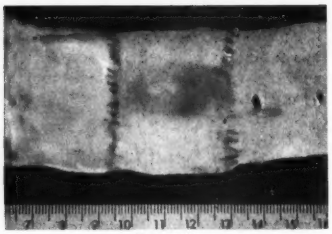

FIG. 10.

FIG. 7. A graft originally constructed of 25 per cent aorta and 75 per cent vinyon 'N.' In this distended state after slaughter, the aortic strips have widened to comprise 50 per cent of the graft's circumference. The graft is straight and isodimensional. The aortic portion of the graft is below the vinyon 'N.' Note the transverse scars in the aortic portion of the graft leading from the longitudinal sutures. These scars represent growth through and from the sutures. The host aorta on the right is tied by a string around a cannula to inflate this graft.

FIG. 8. Intimal surface of a graft originally consisting of 30 per cent aorta and 70 per cent vinyon 'N.' In the distended state after slaughter the aortic strips had widened to comprise 65 per cent of the total circumference. In this opened state, the host aorta and aortic strips have recoiled. The vinyon 'N' is centrally located. Its intimal surface is smooth and glistening. The mottled appearance is due to variable thickness of fibrous tissue overlying it.

FIG. 9. An example of bowing of the aorta and graft in a graft using more autogenous aorta than vinyon 'N.' This is the most marked bowing in the series and does not appear deleterious. The aortic strips have grown in width so that the graft and aorta are isodimensional. Lengthwise growth of the aortic strips has caused the bowing. The vinyon 'N' is on the concave aspect of the bow.

FIG. 10. Intimal surface of a graft originally consisting of 70 per cent artery and 30 per cent vinyon 'N.' In the distended state after slaughter the aortic strips had widened to comprise 80 per cent of the graft's circumference. In this opened state, the host aorta and aortic portion of the graft have recoiled. The vinyon 'N' portion of the graft is the darker central segment. The graft and aorta are isodimensional.

of the graft constituted the concave aspect of this bow (Fig. 9). In no instance did this bowing appear deleterious. No aneurysms of the aortic strips contributing to the bowing were observed. Furthermore, the bowing was most severe in those grafts in which vinyon 'N' constituted only 25 per cent of the circumference of the graft. In those grafts with vinyon 'N' comprising 75 per cent of the circumference, bowing was either absent or very slight (Fig. 7).

The vinyon 'N' portions of these grafts presented the same characteristics as described in series A. However, there was a lower incidence of pleating and calcification. Only 4 of the 13 grafts showed pleating, and this was less severe than occurred in series A. It is assumed that lengthwise growth of the aortic strips sutured to the vinyon 'N' minimized shortening of the cloth. Only 5 of the 13 grafts showed calcification adjacent to the vinyon 'N,' and in general the calcification was less extensive than in series A. This decreased incidence and amount of calcification in series B is unexplained.

DISCUSSION

The dynamics of blood flow as related to growth or lack of growth, and to constrictions or obstructions in the human thoracic aorta are far from known. We do know that coarctation, which represents an almost total obstruction, eventually proves deleterious. We do not know the amount of constriction necessary to produce ill effects. How much may an adult human aorta be obstructed before the obstruction becomes harmful? How much permanent obstruction, or failure of growth, of a child's aorta must be present eventually to result in pathologic changes?

The fact that these questions cannot be answered at present stimulated this study. The ideal aortic graft in a growing aorta should grow as that aorta grows. A method

is presented for attaining this growth of an aortic graft. It is encouraging that the best results (i.e., the straightest isodimensional grafts) in these experiments occurred in those grafts in which the original circumference was approximately 75 per cent vinyon 'N' and 25 per cent autogenous artery. Applied clinically, this means that the required amount of autogenous artery is usually available. Depending on the individual situation, an enlarged internal mammary artery could be opened longitudinally and placed in the graft. Circumferential or longitudinal strips of the subclavian artery could be used. Even circumferential sections from the ends of an excised coarctation might occasionally furnish a supplement to the autogenous portion of some grafts.

Besides the factor of growth, these grafts of vinyon 'N' supplemented with aortic strips appear well suited for long term existence. In this respect they seem superior to the present results of homografts. The dangers of severe degenerative changes are relatively absent. Therefore, when a patient requires a successful long term result, and by long term is meant 40 to 50 years or more, experimental observations indicate that such long term results may be more successfully achieved with inert flexible plastic cloth than with homografts. If the growth factor proves clinically insignificant, the autogenous arterial strips may be omitted from the graft, and a straight tube of cloth used alone.

This study was started in February 1954, when only vinyon 'N' was known to us. Although new cloths became available during this study, the exclusive use of vinyon 'N' was continued so that the experiments might remain constant in this respect. The last evaluation of the various cloths has by no means been made, and improvements will continue. The use of teflon cloth in our laboratory seems encouraging at present.

SUMMARY

1. The present results of arterial homografts manifest essentially two undesirable features. They usually do not keep pace with the growth of the host aorta, and they usually develop degenerative changes which may threaten their long term success.

2. Autogenous arterial grafts yield excellent results, but their use is restricted because of limited availability. Autogenous venous and pericardial grafts are not consistently successful, and thus their clinical use is hazardous because of frequent aneurysm formation.

3. In an attempt to improve this situation, vinyon 'N,' an inert flexible plastic cloth, was used to bridge thoracic aortic defects in weanling pigs. Two types of grafts were made: series A, tubes of vinyon 'N' alone (14 animals), and series B, tubes of vinyon 'N' supplemented with strips of autogenous aorta (18 animals). In series B, the ratio of vinyon 'N' to autogenous aorta in the total circumference of the grafts was varied. The grafts were examined after slaughter some 7 months postoperatively when full growth was attained.

4. Two of the 14 grafts in series A were unsuccessful. One was thrombosed (considered a result of technical error) and the other specimen showed a huge aneurysm of the aorta just distal to the graft. The graft was patent, however, and the aneurysm may have resulted from severe postoperative wound infection. Two of the remaining 12 died of unrelated causes before growth was attained. These two grafts were successful. The other 10 grafts were also successful. They were patent and free of constrictions or aneurysms. Their intimal surfaces were smooth and glistening, and free of ulcerations or thrombi. The vinyon 'N' remained intact and was imbedded in dense scar. A very thin layer of calcification was usually present immediately adjacent to the vinyon 'N' but did not exert a deleterious effect on the intima. The grafts were rigid and inelastic, and, of course, did not keep pace with the growth of the host aorta. Presumably, due to lengthwise growth of the aorta, some grafts were shortened with accordionlike pleating of the vinyon 'N.' Scar tissue filled in these pleats so that the intima was smooth and unwrin-

kled. Pleating did not significantly decrease the graft lumen.

5. All 18 grafts in series B were patent. However, 1 graft at slaughter was complicated by a false aneurysm from a leak at the proximal anastomosis, and another graft showed calcification of the autogenous aortic strip and adjacent host aorta. In addition, 3 pigs died of unrelated causes before growth was attained. Their grafts were successful. The remaining 13 grafts were also successful as regards the object of this study. The autogenous aortic strips grew in width, so that the growth of the anastomoses and graft kept pace with the growth of the host aorta. This growth of the graft occurred regardless of the original proportion of vinyon 'N' and aortic strips comprising the total graft circumference. Lengthwise growth of the aortic strips resulted in slight longitudinal bowing of those grafts with wide aortic strips. Bowing was slight to absent in those grafts made with narrow aortic strips. The vinyon 'N' portion of these grafts presented the same characteristics as in series A, although pleating and adjacent calcification was much less frequent and severe.

CONCLUSIONS

1. The long term success of aortic homografts in children and young adults is questionable. Clinical homografts probably do not grow with the host aorta and may develop severe degenerative changes.

2. In overcoming these undesirable features, the use of autogenous artery is restricted from a practical standpoint by its unavailability. Autogenous vein, pericardium, and other tissue are dangerous because of possible aneurysm formation.

3. A graft of vinyon 'N' supplemented with a longitudinal strip of autogenous artery grows circumferentially with the host aorta, and is free of the deleterious effects of degenerative change. The amount of autogenous artery needed is small enough for clinical availability.

4. When growth is not a significant clinical factor, the use of inert flexible plastic cloth alone is probably preferable to homografts for long term success.

5. The use of either homografts or plastic cloths alone may still be considered experimental. Improvements with both will continue.

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SPLENOPORTAL VENOGRAPHY

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THE MOST EFFECTIVE surgical procedure for the relief of portal hypertension and its serious sequella, esophageal hemorrhage, is a venovenous shunt between the portal and systemic venous systems. Choice between the direct portacaval shunt and the less direct splenorenal shunt is at times determined by the personal preference of the surgeon but at other times the anatomic arrangement of one of the veins or its thrombotic obliteration does not afford the opportunity to choose. Knowledge of the site and patency of the portal and splenic veins obtained before the operative incision is made can do much to expedite the operative procedure. If an occluded portal vein, or if a bifid or undersized splenic vein can be demonstrated preoperatively the incision can be intelligently placed and a direct approach made to the more suitable vein.

When contrast material is introduced rapidly into the splenic parenchyma, it is picked up by the venous channels draining the spleen and carried into the portal venous system. By rapid serial roentgenography the opacified splenic and portal veins may be visualized.

Percutaneous or transparietal puncture of the spleen for diagnostic biopsy in cases of hematologic and splenic disorders has been practiced, at least since the latter part of the nineteenth century when Vidal is credited with the performance of the first splenic puncture. Use of splenic puncture for radiographic opacification of the portal venous system was introduced by Abeatici and Campi in Italy in 1951. The value of this procedure was immediately recognized and adopted in Europe and in this country. Reports by Rousselot and Cooper and their associates point out the value of this examination in the study of the anatomy and pathology of the portal venous system.

In the venographic study of the portal system in this center, rapid serial radiography has been used. A roll film magazine with 12.5 by 12.5 inch film is utilized and this film size is adequate for any patient properly positioned on the cassette. Two features of rapid serial films are of real value. Primarily one may be sure in studying the series of films that failure of a vein adequately to opacify is not due to poor timing of the roentgen exposure but is due to a real defect or thrombus in that vein. In several films in any one series the portal vein is poorly or weakly opacified. To differentiate this from a partly recanalized thrombus would be difficult without the immediately subsequent films which show clear, full opacification of the vein. The time spread in this technique eliminates the possibility of inadequate opacification due to poor timing. Another valuable feature of the rapid, serial technique is its ability to picture the sinusoidal phase of hepatic opacification. In this phase the liver stands out, alone, uniformly opacified, and defects caused by primary or metastatic tumor may be seen. An additional facet of interest in this technique is that it provides opportunity to follow the physiologic, dynamic direction of the flow of blood in the portal venous system. A series of films taken at ½ or 1 or 2 second intervals gives one a picture of movement and direction beyond mere anatomic arrangement. The retrograde flow in the portal tributaries is well shown. The detailed report of the x-ray technique is to be reported elsewhere (5).

Our series consists of 23 studies in 21 patients, 2 with normal portal systems but with splenomegaly secondary to a blood dyscrasia, 17 with portal hypertension, and

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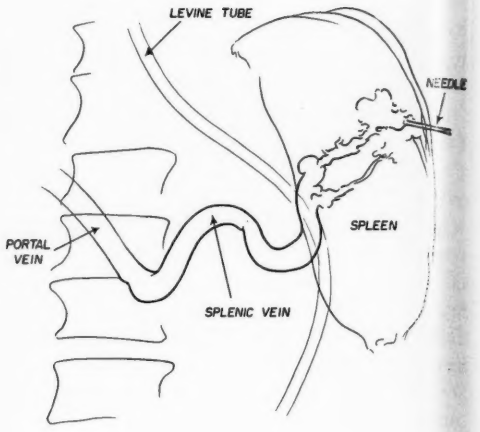


FIG. 1. J. D., NYH64 16 27. This patient had a severe anemia, thrombocytopenia, and an enlarged spleen. Portal pressure was normal. This x-ray film is representative of a normal study. No tributaries are visualized and the contrast medium was cleared from the portal vein in 5 to 6 seconds. The injection itself is not ideal as much contrast medium has been deposited subcapsularly. A Levin tube is in place in the stomach.

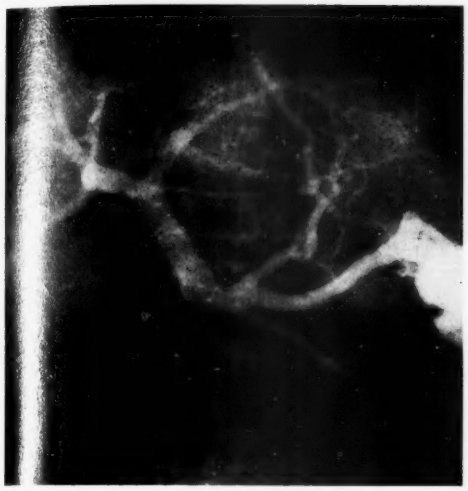
2 with intra-abdominal tumors. One patient in the portal hypertensive group was studied both before and after the portacaval shunt.

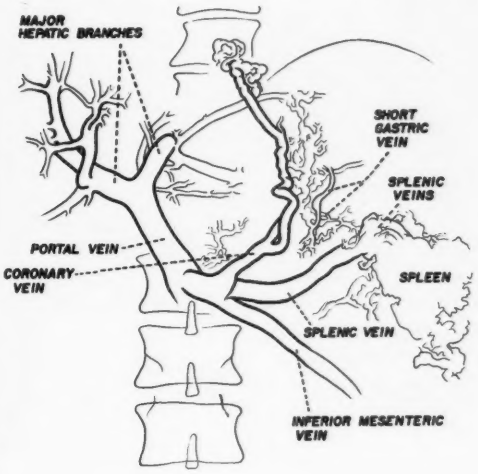
TECHNIQUE

The great majority of the studies, 18, were performed under general anesthesia immediately prior to surgery. Five studies were done as independent procedures under local anesthesia. The present technique is to introduce a No. 17 needle, without an obdurator, through the ninth intercostal space in the midaxillary or posterior axillary line. When the needle is well in the splenic parenchyma blood will flow slowly from it. A short length of polyethylene tubing unites the syringe to the needle. This tubing permits the needle to move with the spleen should the patient breathe while the injection is being made. Thirty to 50 cubic centimeters of 70 per cent urokon are injected as rapidly as possible. Roentgenograms are taken as the injection begins and continued for 12 to 15 seconds. Exposures made at 1 second or 2 second intervals are sufficient to provide complete coverage.

RESULTS

In 3 of 23 attempts the portal venous system was not visualized. One patient had a huge multilobular retroperitoneal lymphoma and his spleen had not been localized before the attempted study. The spleen was not punctured and no venous visualization was obtained. An exploratory operation was performed and biopsy of the tumor made. No evidence of intraperitoneal damage was found at operation. The second man had a gastrointestinal hemorrhage 3 months after a portacaval shunt. He was studied after he had recovered from this episode. The needle was inserted under local anesthesia but it was passed through the spleen and the urokon was deposited in the peritoneal cavity. The next hour the patient had a great deal of left upper quadrant pain which was aggravated by respiration. After this initial hour the pain rapidly subsided. He was restudied 2 days later and a patent





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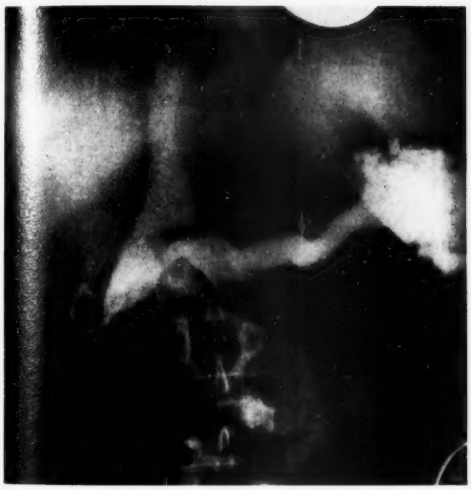

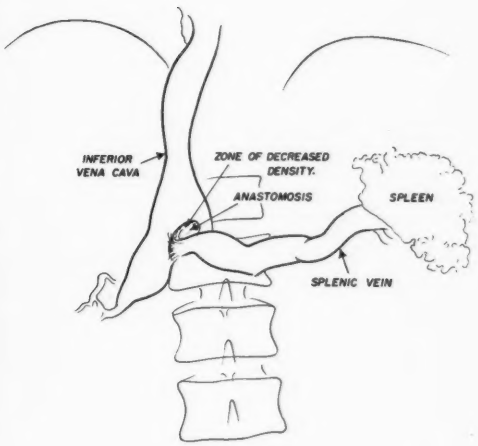

b

FIG. 2. W. McG., NYH67 31 36. a, X-ray film from a series done preoperatively in a patient with Laennec's cirrhosis. Patent portal and splenic veins may be seen. In addition, portal tributaries, the coronary vein, the short gastric veins, and the inferior mesenteric vein are opacified by retrograde flow. The superior mesenteric vein does not fill. b, The same patient has had an end-to-side portacaval shunt since the previous examination. The contrast medium now flows directly into the vena cava and no tributaries are opacified.

shunt was demonstrated (Fig. 2b). The third patient, a cirrhotic, was studied immediately preoperatively. Her operation was performed as an emergency with the inflated Sengstaken-Blakemore balloon in the esophagus. The introduction of the needle was without incident and its position seemed satisfactory. Forty cubic centimeters of 70 per cent urokon were injected. When the x-ray films were developed the urokon formed a single large shadow in the left upper quadrant. There was no intravenous

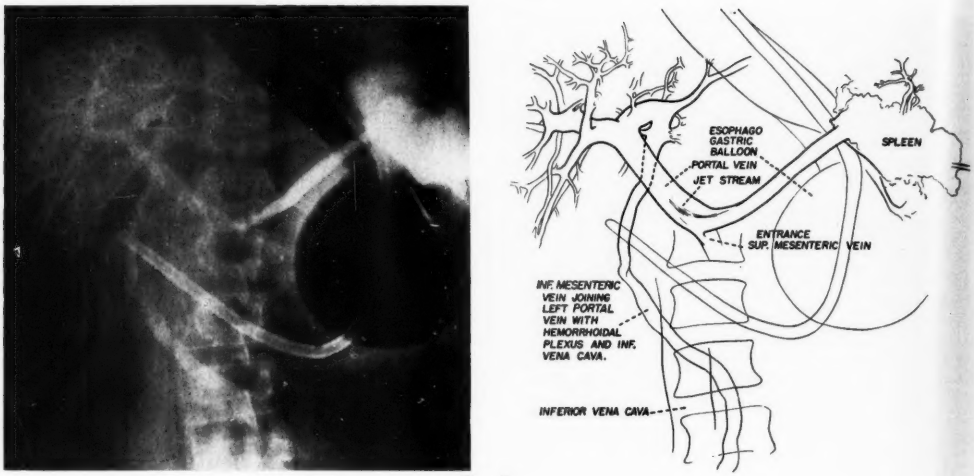
ESOPHAGO GASTRIC BALLOON
PORTAL VEIN JET STREAM
SPLEEN
ENTRANCE SUP. MESENTERIC VEIN
INF. MESENTERIC VEIN JOINING LEFT PORTAL VEIN WITH HEMORRHOIDAL PLEXUS AND INF. VENA CAVA.
INFERIOR VENA CAVA

FIG. 3.

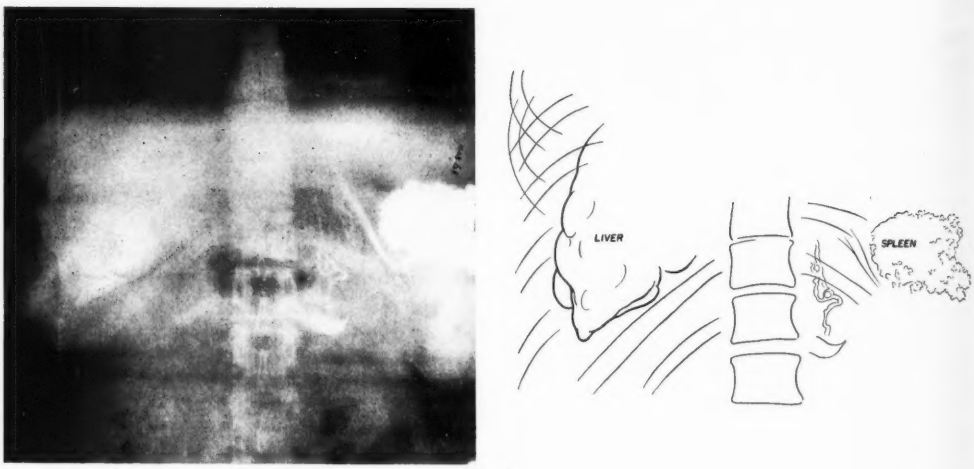

FIG. 4.

FIG. 3. E. M. NYH67 88 42. Splenoportal venogram is from a study of a young cirrhotic patient. The coronary vein and esophageal tributaries do not fill, presumably because of compression of the esophageal veins by the inflated Sengstaken-Blakemore balloon. An anomalous inferior mesenteric vein may be seen which empties into the left branch of the portal vein.

FIG. 4. M. N., NYH66 76 53. X-ray film of a patient with a small nodular liver and massive ascites, taken rather late in the series of films and showing the excellent opacification of the liver itself. The nodularity of this organ is apparent.

pick up of the contrast medium. When the spleen was exposed the site of the needle puncture was visualized and was properly placed. No explanation for the failure of the veins to pick up the urokon is apparent.

All other studies resulted in adequate visualization of the portal venous system. Samples of the x-rays obtained are presented in Figures 1 to 6. Figure 1 is representative of a normal study. No tributaries are visualized, the contrast medium travels rapidly into the liver and disappears after 5 or 6 seconds. Figure 2a shows the characteristic picture of a cirrhotic patient with portal

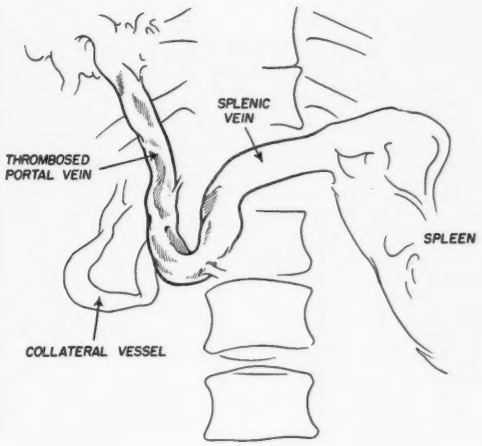

FIG. 5. E. W., NYH55 25 27. The x-ray film shows the irregular, blotchy filling of the portal vein. If this portal vein was seen in an x-ray film obtained by the single exposure technique, it might be difficult to be certain that a thrombus was present. Inadequate filling of the portal vein may result from poor timing of the x-ray exposure. In the serial x-ray study of this patient the blotchy appearance of the vein was constant throughout. At operation an extensive thrombus was found in the portal vein.

hypertension. The contrast medium flows retrograde along many portal tributaries. Figure 2b is the same patient after an end-to-side portacaval shunt. The contrast between Figure 2a and 2b is apparent. Figure 3 is from a study of another cirrhotic; again the tributaries of the portal vein fill, including an anomalous inferior mesenteric vein that drains into the left branch of the portal vein. The esophageal tributaries are compressed by the inflated Sengstaken-Blakemore balloon and are not visualized. Figure 4 shows a small, nodular liver in a patient with ascites. The degree of hepatic opacification is not unusual and shows how well the liver may be visualized. Figure 5 shows a partially recanalized thrombus in the portal vein. Figure 6 is from the study of a patient suspected of having a pancreatic tumor. The x-ray series demonstrated local involvement of the midportion of the splenic vein and a filling defect in the right lobe of the liver. At operation a tumor was found in the body of the pancreas and a metastatic nodule was seen in the right lobe of the liver.

Only 1 patient in the group operated on immediately after the splenic puncture had active bleeding from the spleen when it was visualized. This patient was 1 of the 2 controls, without portal hypertension but with splenomegaly associated with severe pancytopenia and thrombocytopenia. In this patient splenectomy was the planned procedure and it was done. In every other instance the bleeding had ceased by the time the spleen was exposed. Blood loss averaged about 75 cubic centimeters. In 2 instances the loss was 200 cubic centimeters or more; in several cases no blood was found. In none of the studies done under local anesthesia was there any evidence of intraperitoneal bleeding.

DISCUSSION

The value of adequate knowledge of the size and patency of the portal and splenic veins before attempted surgical correction of portal hypertension is obvious. Percutaneous splenoportal venography utilizing rapid serial radiography gives this informa-

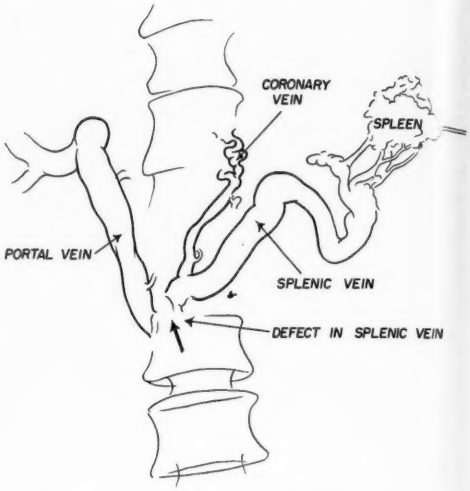

FIG. 6. G. S., NYH69 64 33. This patient had metastatic, undifferentiated carcinoma in a cervical lymph node, a suspicious x-ray shadow in her lung, and obstructive jaundice. The splenoportal venographic study was performed several days prior to laparotomy. The x-ray film shows some interference with blood flow in the midportion of the splenic vein (arrow), with ancillary evidence of obstruction of the vein at this point. The ancillary evidence is the retrograde filling of the tributaries of the splenic vein and the delay in disappearance of the contrast medium from the splenic vein. In the phase of sinusoidal filling when the liver is uniformly opacified a defect or local area of nonopacification is identified near the edge of the right lobe of the liver. At operation a tumor mass was found in the body of the pancreas and a large metastasis in right lobe of liver.

tion. In addition, this technique provides excellent opacification of the hepatic parenchyma and will doubtless prove useful in visualizing metastatic or primary tumor in the liver as well as giving evidence of involvement or displacement of the splenic vein by tumors in the region of the pancreas.

In several patients roentgenologic examination was made and operation performed as an emergency with an inflated Sengstaken-Blakemore balloon in the esophagus. In these patients the esophageal tributaries of the portal vein were compressed and did not opacify. In every other case of portal hypertension retrograde blood flow was noted in the short gastric veins, the coronary vein, and the inferior mesenteric vein. No retrograde flow was seen in the superior mesenteric vein. One may speculate that the portal tributaries with peripheral exits in the nature of normal anatomic connections with the azygos and hemorrhoidal systemic veins permit retrograde flow; but the superior mesenteric vein has no such connections and, therefore, retrograde flow in it is impossible.

The value of the technique is established. The risk must then be considered. Inherent in the puncture of as vascular an organ as the spleen is the risk of hemorrhage. Morrison and associates, in reporting 105 splenic punctures for hematologic study, concluded that it is an innocuous procedure. Chatterjea and associates reported 43 similar punctures without complications. Block in a carefully studied summary of 92 splenic punctures reported no fatalities from hemorrhage from the spleen, but 4 instances of bleeding of a magnitude requiring replacement by blood transfusions. Two who bled were classified by Block and Jacobson in the hepatosplenomegaly (Banti's syndrome) group.

So the procedure of splenic puncture does, as anticipated, carry some hazard. This, we believe, is not great, and can be rapidly recognized and properly treated if

it occurs. The value of the study when properly indicated and carefully performed outweighs the risk. Much of real importance to the patient can be learned by splenoportal venography combined with rapid serial radiography. In this short series no significant complications were encountered and reliable information was obtained when it was most valuable, before the incision.

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EDITORIAL

INTRAPERITONEAL DRAINAGE, WHEN AND HOW?

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INTRAPERITONEALLY PLACED DRAINS have been used since the earliest days of surgery. When used to drain definite accumulations of pus, their presence is essential. However, when placed to provide a pathway along which anticipated leakage might find egress from the peritoneal cavity, they have seemed to surgeons to represent foreign bodies which are quite frequently unnecessary. Since there are many instances in which drains are placed and no drainage occurs, there is a constant tendency to avoid them. Such an attitude is not only justified by the fact that anticipated drainage rarely occurs, but by the experimental evidence that intraperitoneally placed drains are walled from the preperitoneal cavity within a matter of hours.

The widespread adoption of three factors in surgery has lessened the likelihood of unwanted and late drainage from the gastrointestinal tract. These may be listed as: first, the use of nonabsorbable sutures on the outer layer of all gastrointestinal anastomoses; second, the preoperative use of gastrointestinal antisepsis; and, third, the administration of wide spectrum antibiotics during the postoperative period of convalescence.

In spite of these factors, surgeons must not forget that if intraperitoneal drainage does occur, death is likely to result. It is, therefore, particularly important that surgeons anticipate with accuracy the probability of the development of leakage of material from the gastrointestinal tract. In each case in which they operate and such a leak is likely to develop, the provision of drainage must be considered. If used, such drains should establish a tract along which any material which is present at the time of surgery or which later on may leak from a hole in the gastrointestinal tract may find its way to the outside of the body. Such a form of drainage may well be referred to as provisional drainage.

The operations for which provisional drainage should be anticipated may be roughly listed as follows: (1) operations upon the biliary tract in which invisible bile canaliculi may not be seen leaving the liver, or during which secure closure of the common duct is not possible; (2) anastomoses or openings into the structures of the gastrointestinal tract whose anatomic position within the peritoneal cavity is likely to be stationary; (3) operations upon portions of the gastrointestinal tract whose walls are not adequately covered with tough and firm adventitia; (4) those whose topographic relationships and anatomic connections are such that they do not permit such free and easy mobilization as to allow a surgeon to reduce tension on the suture line in a totally satisfactory manner.

In the first group of conditions, as indicated, we include all operations upon the biliary tract; in the second group, operations which leave the stump of the duodenum, such as the Polya type of gastric resections. Tears of the gastrointestinal tract, such as occur after blunt injury to the abdomen and in rupture of the duodenum,

may require drainage because the actual viability of the edges of the ruptured bowel cannot always be accurately assessed at the time of surgical repair. In these instances, the presence of active digestant duodenal contents within the lumen of the gut is a constant threat to any technical irregularity or weakness. In anastomoses between the ileum and the colon, particularly as after right colon resections, the irregularity between the two different structures which are anastomosed presents a technical problem. The third group includes anastomoses between the ends of the colon and the extraperitoneal areas, and anastomoses between the pancreas and the jejunum as after pancreaticoduodenectomy and as in caudal pancreaticojejunostomy. The fourth group includes gastroduodenal anastomoses, as after Billroth I operations in which tension may be present. Needless to say, there are many instances in which more than one indication for the provision of drainage is present.

Several basic physical factors must be observed in order to be sure that drainage which does occur will drain to the outside. In the first place, enough drains must be provided to establish a tract. This tract should allow and encourage any fluid which may accumulate within the peritoneal cavity to find an easy egress to the outside. Since a hollow tube is likely to become sealed off in a very short time, such a hollow tube obviously will not be satisfactory. If two Penrose drains are placed together, however, many folds will develop between them. These folds will result in spaces which are free from the encircling omentum and loops of bowel. These spaces act as a tract along which any intraperitoneal fluid is likely to find its way to the outside.

Secondly, the surgeon must be absolutely certain that drains properly placed remain at the site which they are expected to drain. This can only be accomplished by suturing them in place. Extremely fine catgut, such as No. 6-0 plain catgut suture, should be used. Drains so secured in the neighborhood of vital structures, of course, should not be sutured to any structure which could be torn if they were accidentally pulled. These drains can usually be secured to the fat tissue in the nearest portion of the abdominal wall. Although such drains cannot be removed with ease during the first few days, probably they should not be removed during this period. If very fine catgut suture is used, it will be absorbed by the end of a week or 10 days when these drains may be removed as readily as drains not so anchored. In the occasional case in which drains stay in longer than 6 or 7 days because of the suture material, little harm is done; the patients may be allowed to go home and the drains may be removed on a subsequent visit.

Thirdly, drains which are anchored and in proper abundance may be rendered completely useless if the closure of the abdominal wall is so secure and so tight that it occludes the lumen of the potential spaces created by the folds of rubber. The author has seen at least 3 such cases. To avoid this complication, the abdominal wall should not be closed snugly around these drains; rather, the opening about the drains should admit the tips of two fingers readily. Thus a stab wound will not provide the adequate free drainage. The very term "stab wound" suggests that the simple passage of a knife blade through the abdominal wall has established this opening. Only hollow tubes, such as a T tube or a catheter whose consistency and form will maintain its own lumen, can be depended upon to be effective through a stab wound.

Most drains placed and used with the precautions listed will be effective. In instances of repair upon the biliary tract, where accumulations of material are expected early, the use of a hollow tube or sump drain, to which suction can be applied, may wisely be added. By the use of this type of drain, the constant emptying effect will encourage any accumulating and draining fluids to escape through the tube and thus accumulation in the peritoneal cavity will be avoided.

By keeping this area totally empty, natural walls of adhesions form and allow walling off of the involved areas from the peritoneal cavity.

The surgeon must be certain to replace all intraperitoneal structures into the position which they are likely to occupy during convalescence before drains are placed in their final position. Otherwise, the resumption of normal position may so kink a drain that it can no longer be effective. Particularly must the liver be placed in the proper position before placing drains to areas about it. If this is not done, when the liver resumes its normal position, drains may be so kinked that they will no longer be effective.

Dependent drainage which is recommended freely and spoken of commonly must be looked at very critically. It is often provided with a stab wound and is consequently apt to be ineffectual. For instance, dependent drainage provided to the area of the common duct would necessitate a rather free and large incision placed in the flank below the twelfth rib. To be effective, bile leaking from the common duct would have to traverse the entire retroperitoneal space and the thick abdominal wall. It would also have to traverse a broad field in which the hepatic flexure of the colon would have a tendency to agglutinate to the underside of the liver. In such cases, this area can be much more effectively drained by the use of several Penrose drains placed through the abdominal incision down to the region of the common duct. It should be kept in mind, however, that in certain selected cases drainage may be needed in several areas (following injuries such as rupture of the liver or gunshot wounds of the liver). Here free and early evacuation of any seeping bile or fluid which may accumulate around the area of liver damage may be lifesaving. To this end not only must drains be placed through the abdominal wall after exploration for liver injury, but frequently drains should be placed above the liver, and deliberately large counterincisions should be made in the flank in the most dependent portion. In such instances, it is also probable that sump drains placed with each group of Penrose drains may facilitate the early evacuation of accumulating fluids.

Occasionally it is possible to utilize intraperitoneal structures in order to isolate areas in the peritoneal cavity. Areas in which leakage and possibly contamination are likely to occur may be isolated, thereby preventing generalized peritonitis, especially in the areas above the transverse colon where the omentum provides a natural structure which may be safely sewed to the sides of the abdominal wall. The entire supracolonic area may thus be isolated from the infracolonic area by suturing the omentum to the abdominal wall; for instance, after gastric resection, when a duodenal stump closure is less than satisfactory, and also in cases in which drainage is expected, as after a Whipple operation, or after repair of multiple lacerations of the liver. In the drainage of a subphrenic abscess, should the peritoneal cavity accidentally be opened, the omentum can often be utilized in this manner and be sewed to the abdominal wall. The natural walling off process can thus be directed.

When drains have served their purpose they, of course, should be removed. Since they do no real harm aside from their presence as foreign bodies, it is rare that drains placed to provide egress of fluid should be removed before 1 week is over. By this time any leakage which is likely should have occurred. Furthermore, by this time a tract will have been laid down by the presence of the drains which will encourage pointing of any delayed drainage. After this period of time, they should be removed. If deep, they should be removed slowly, by being advanced an inch or two each day. We have seen several instances in which small accumulations of pus have occurred in the intraperitoneal side of the drainage tract when removal of the drains was accomplished too rapidly.

THE SURGEON AT WORK

A CONTINUOUS INTERRUPTED EVERTING SUTURE FOR ARTERIAL SURGERY

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THE USUAL METHOD of suturing arteries is with interrupted everting mattress sutures. This method has two disadvantages: Unless the stitches are put very close to each other a small unsutured gap remains in between the stitches, and if one of the stitches should give way a large leak would develop. Consequently, a second continuous suture is usually placed over the artery after the interrupted suture has been completed. This method has the additional disadvantage of a tendency to constrict the anastomosis, particularly if the stitches are inserted beyond the interrupted suture.

The suture to be described is designed to overcome some of these difficulties. Although it is in principle an interrupted everting mattress suture, by virtue of the special technique devised it is in effect continuous, as no part of the arteries remains unapproximated by a suture.

The accompanying diagrams are, we hope, self-explanatory. The main difference between this suture and any other is the fact that 2 threads, preferably of different colors (black and white), are fixed in the eyeless needle (Fig. 1) and are alternatively tied as illustrated in the diagrams.

Figure 2a illustrates the first step of suturing. Two mosquito forceps are fixed to the loose ends (*1* and *2*), and after the suture has been passed through both arteries the black thread is cut and the ends (*3* and *4*) are secured with mosquito forceps. Next the ends of the black thread (Fig. 2b, *1* and *3*) are fastened in one forcep. This black thread is kept untied and will be used last to link up the last stitch closing the lumen completely (Fig. 2e). The suture is then returned as shown in Figure 2b, and the white thread is cut. The ends (*5* and *6*) are secured with mosquito forceps, and the ends (*2* and *5*) are tied. The suture is then returned and the black thread is cut (Fig. 2c, *7* and *8*) followed by tying of ends (*4* and *7*) as indicated. This results in a continuous closure by interrupted everting mattress stitches (Fig. 2d).

When the threads of the first needle have been used up, the suture is continued with a second needle in the manner indicated in Figure 2d. The black thread has just been tied and the new suture passed. The ends of the new suture have been secured with mosquito forceps, and the white thread is then cut between mosquito forceps at the arrow. We now proceed to tie the white threads on either side. The suture is then continued as shown in Figure 2b.

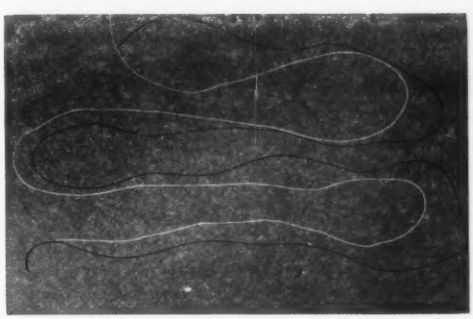

Fig. 1. The actual suture: the eyeless needle with No. 5-0 black and white braided silk.

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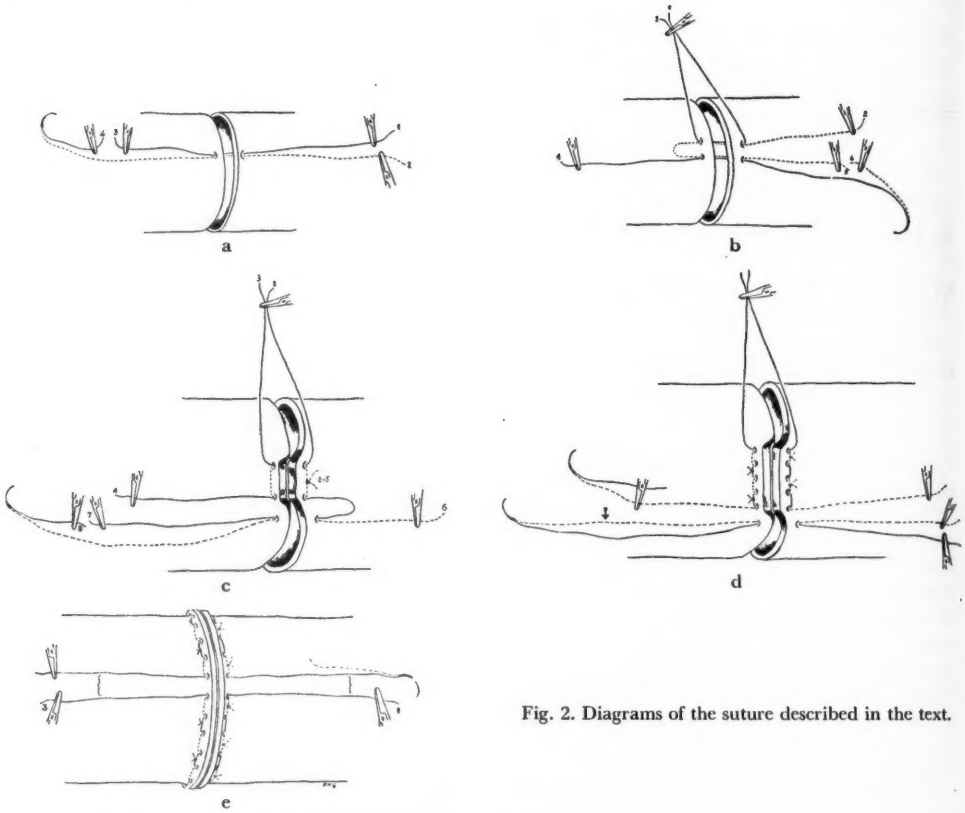

Fig. 2. Diagrams of the suture described in the text.

The advantages of the proposed suture are manifold: (1) A completely watertight union can be effected at first intention. (2) No further suture need be placed over the original everting suture, thus avoiding constriction of the anastomosis. (3) If any one of the sutures should give way, the gap resulting is no larger than that normally present between the stitches of the ordinary mattress suture. (4) The suture, although perhaps appearing complicated at first sight, is simple, time-saving, and with a minimum amount of stitches a maximum amount of sutures are applied.

The suture has been employed in various procedures, including coarctation of the aorta, and has been found to be satisfactory. It can also be applied in other than vascular surgery.

If an atraumatic needle is not essential, strands, the 2 halves of which are of different colors, can be used. The sutures are available in black and white sizes No. 3-0 or No. 5-0 U.S.P. braided silk and on various needles.

The Book Shelf

ADVENTURES IN INTUBATION

GEORGE J. D'ANGELO, M.D., Durham, North Carolina

THE ART OF INTUBATION dates from antiquity and its development presents an important chapter in the advancement of gastroenterology. Those who are eager to know the details of the history of the stomach tube should consult the excellent paper by Friedenwald and Morrison. My purpose is to bring to the busy physician the highlights of this adventure without drawing upon the minor incidents. However, one must not forget that the supposedly inconsequential events played an important role in the development of intubation.

Long before the advent of any tube the simplest procedure by which to expel the gastric contents was to place a finger in back of the tongue to stimulate the vomiting reflex. Because such an act was crude the rulers of Rome who feasted for days introduced a vomiting feather. This feather was called a "pinna" and was used in place of the finger. The Romans made use of the pinna in order to make room for further meals. This was all done without getting up from the table, since the servants would bring forth the vomiting pail when beckoned. Often the pinna alone was not effective; therefore, it was dipped into iris or cypress oil which not only made it more nauseating but also more efficacious. "It was as the result of the application by his physician of such a feather to which poison had been applied that Claudius succumbed at the instigation of Agrippina" (3).

Galen (130–200 A. D.) in his treatise *The Physician* mentions the use of a catheter, devised by Erasistratus of Alexandria (circa 300 B. C.), to empty a full bladder. In spite of his prolific writings and basic research, he fails to mention any use of a stomach tube.

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Perhaps, the forerunner of the stomach tube is the one devised by Oribasius (325–403 A. D.). He gives the following description as a method of inducing vomiting: "Glove fingers are stitched together . . . the length of ten or twelve fingers, like a finger, six fingers length is stuffed with wool, the rest . . . length of four fingers remains empty; it is applied to the finger, . . . is smeared with ointment and introduced into the stomach" (9). It is doubtful whether such a sound ever reached the stomach, for vomiting would surely occur long before very much of this tube passed the epiglottis. Any superiority to the pinna is extremely skeptical. Nevertheless, it opened up a new road. There are numerous modifications of this device, which were referred to as "lorum vomitorium."

The three methods mentioned, digital, pinna, and lorum vomitorium, were all used to provoke vomiting in order to empty the stomach of its contents, whether it be food or poison.

The interest swung from evacuation of the gastric contents to introducing food into the stomach. Among the first to take this step was Johann Arculanus, professor at Bologna and Padua, who in 1493 described an instrument for forcing food down into the stomach. At this point mention must be made of Thomas Willis' (1621–1675) celebrated case. His patient "cast up whatsoever he had eaten . . . when that no medicines could help, and he languished away for hunger . . . I prepared an Instrument for

him like a Rod, of a whale Bone, with a little round Button of Sponge fixed to the top of it; the sick man having taken down meat and drink into his throat, presently putting this down in the *Oesophagus*, he did thrust down into the ventricle, its orifice being opened, the food which otherwise would come back again; and by this means he hath daily taken his sustenance for sixteen years . . . without doubt in this case the mouth of the stomach being always closed, either by a Tumour or Palsie, nothing could be admitted into the ventricle unless it were violently opened." Many after reading this description would shudder at such a treatment, but there is no need to believe that Willis was barbaric. Just consider the bougies used to dilate lye strictures of today, then you will realize that Thomas Willis would be welcomed in our clinics.

In spite of the crude instruments, progress was being made. The pendulum next swung to a means of removing foreign objects from the esophagus. The Father of German Surgery, Frabicius Hildanus (1560–1634), used a metal perforated tube with a small sponge attached to its lower end for removal of foreign bodies from the esophagus. With this he was successful in extracting numerous fish bones, etc., of which he had a nice collection. He, however, did not devise the tube, for he gives this priority to Walter Ryff for the discovery of this instrument, which is described in Ryff's *Magna Chirurgia*.

About the same time Fabricius ab Aquapendente (1537–1619) was confronted with a patient who could not eat because of locked teeth. Since "necessity is the mother of invention," Fabricius made "a tube of silver, a little curved, we make the liquid nourishment pass by the nostrils to the palate, and it is a good method, particularly if one covers the tube with sheep's intestine (cannula aguino intestinulo)." Prior to this, such patients were either left alone to die or attempts were made to feed liquids through a funnel placed where there was a missing tooth or to extract several teeth.

Thus far, advancement progressed along practical and perhaps scientific avenues, but this must come to a standstill temporarily to make room for the faddist. Suddenly, throughout Europe many dignitaries would travel days to reach the secret clinics where they could have their stomachs cleansed with a stomach brush. This consisted of a long, smooth, flexible whalebone to one end of which was attached a tuft of silk cord or horsehair. After it was introduced into the stomach the brush would be rotated and pushed back and forth while the patient drank water intermittently in order to thoroughly cleanse the stomach. One treatment was not enough but had to be repeated for 3 or 4 consecutive days. Its popularity rose because it was practiced in secrecy. However, as all fads it had its demise on account of the many fatalities which were inevitable. The South American Indians treated disorders of the stomach with a similar instrument, except that they used "rope made of padded sharp leaves" (3).

With the stomach washing adventure just a memory, the name of Hermann Boerhaave (1668–1738) is often connected with the introduction of the stomach tube. Although in his writings he cites that a flexible metallic tube should be introduced into the stomach for irrigation in cases of poison, he does not allude to the fact that he ever made use of it.

What Boerhaave failed to do, John Hunter (1728–1793) accomplished. This illustrious genius on March 21, 1776, read a paper making use of a stomach tube in persons undergoing artificial respiration, so that medicines could be administered without injury to the lungs. He advised that through the nose a "hollow bougie, or flexible catheter, of sufficient length to go into the stomach, and convey any stimulating matter into it, without affecting the lungs," be passed (7). Again on March 9, 1790, he contrived for a patient with paralysis of his deglutition muscles an instrument, "a fresh eel-skin, of rather a small size, drawn over a probang, and tied up at the end where it covered the sponge, and tied again close to the sponge where it is fastened to the whalebone, and a small longitudinal slit was made into it just above this upper ligature. To the other end of the eel-skin was fixed a bladder and wooden pipe, similar to what is used in giving a clyster, . . . The probang, thus covered was introduced into the stomach, and the food and medicines were put into the bladder, and squeezed down through the eel-skin" (6). No wonder John Hunter has been claimed the inventor of the stomach tube by Garrison.

Slowly the stomach tube became to be used more and more. Up until now, the tube served as a means of introducing matter into the stomach. However, in 1797 a thesis, "De Dysphagia," written by Alexander Monro III (1773–1859) in which he claims that 30 years before, his father,

Monro II, employed a flexible tube with bellows and speculum oris for removing dangerously fermenting fluids and gases from the stomachs of cattle.

van Helmont in 1644 discovered a method for manufacturing flexible leather catheters but their usefulness was not recognized until over a century later. It became a most useful tool as illustrated by a case of Baron Larrey (1776–1842), surgeon-general for Napoleon. A soldier, Marshall Murat, was shot in the throat at the Battle of Aboukin in 1801 and by passing a flexible tube into the stomach his life was saved. Larrey determined the tube's position by injecting a few drops of water to see if the patient coughed, if not he proceeded to feed him.

Now we cross the Atlantic Ocean for further development in this adventure. Ignorant of the preceding work, Philip Syng Physick (1768–1837) of Philadelphia since 1800 had been washing out the stomach with syringe and tube. On June 6, 1812, he was called to see twins who were suffering from whooping cough and inadvertently poisoned with laudanum. He was able to save one of them by means of aspiration of the gastric contents with his tube and syringe. Let us return to England where in 1822 there was a friendly feud taking place between Edward Jukes of Westminster and Frances Bush of Frome as to the priority of the "stomach pump." Both advocated the use of a flexible tube but Jukes attached an elastic bottle whereas Bush employed a syringe as a means of aspiration. Regardless of who is given credit for the invention of the "stomach pump," the fact that it existed helped to move back the frontiers.

The interest in the stomach tube began to wane until Kussmaul revived interest with his classic paper in 1869 (2). This paper is supposed to have been responsible for Billroth's interest in gastric surgery (8). With this revival, the pendulum swung to the diagnostic possibilities with the use of the stomach tube. Leube in 1871 suggested the use of the test meal (2).

A long list of men followed, of which I shall mention a few, in making the stomach tube better for the patient to tolerate, and simultaneously the advancement of gastric physiology took place. Ewald developed a soft pliable rubber tube. Marcy instituted a double irrigation tube. Hemmeter attempted to intubate the duodenum. With these pioneers to pave the path, great strides were made in the study of gastrointestinal diseases. Perhaps the tube will never be replaced for certain disorders such as intestinal distention but for the study of gastric physiology there is a movement in progress to do away with intubation and to substitute biochemical means.

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6. Hunter, John. A case of paralysis of the muscles of deglutition, cured by an artificial mode conveying food and medicine into the stomach. Tr. Soc. Improv. Med. and Chir. Knowledge, 1793, 1: 182.
7. Idem. Proposals for the Recovery of Persons Apparently Drowned. Works of John Hunter. Vol. IV, p. 173. London: Longman *et. al.*, 1837.
8. Lyon, B. B. V. Few notes on introduction and development of duodenal tube. Tr. Am. Gastroenter. Ass., 1927, 30: 34.
9. Major, Ralph H. History of the stomach tube. Ann. M. Hist., 1934, 6: 500.
10. Marcy, A. O. Double irrigation and drainage tube. N. York M. J., 1883, 37: 629.
11. Physick, P. S. Account of the new mode of extracting poisonous substances from the stomach. Eclectic Repertory and Analytical Rev., 1812, 3: 111, 380.
12. Willis, Thomas. Pharmaceutice Rationalis Sive Diatriba de Medicamentorum Operationibus in Humano Corpore. Oxoniae, 1674–1675.

Reviews of New Books

THE BOOK entitled *Standard Values in Nutrition and Metabolism*[1] was produced under joint sponsorship of the Air Force, Army, Navy, and Atomic Energy Commission as Wright Air Development Center Technical Report 52–301. The work was directed by the Committee on the Handbook of Biological Data, an organ of the American Institute of Biological Sciences which is affiliated with the National Research Council.

This tabular monograph is the product of contributions of more than 800 specialists in nutrition, metabolism, and related fields. There are 160 tables that were reviewed extensively by experts on the respective subjects. All controversial or questionable or borderline matter was removed from the tables leaving only material accepted as fact. The 223 pages of tables and 16 pages of diagrams contain many thousands of items of authoritative data, most of which is quantitative.

The tables are grouped into 13 main divisions which are as follows: nutrients; nutrients utilized by animal forms; nutrients utilized by plant forms; daily nutrient allowances (animal forms); diets, culture media, for animal forms; culture media, fertilizers, for plant forms; nutrient and energy values of foodstuffs and feedstuffs; nutrient functions and signs of deficiency and excess; pathways of metabolism; end products of metabolism; oxygen consumption, carbon dioxide production of plant tissues and organisms; and energy exchange. There is an extensive bibliography and index.

This is an excellent reference book containing undisputed data on nutrition and metabolism.

—*Opal Hepler.*

THE AUTHORS of *Maladies des os et des articulations*[2] present inclusive material on the pathology of bones and joints in an extremely interesting and orderly manner. The book is divided into 3 parts, namely, pathology of the bony tissues and bones (14 chapters), pathology of the joints (7 chapters), and pathology of para-articular tissues (5 chapters).

A brief review of the morphology, physiology, and growth of bony tissue is followed by a discussion on the anatomic and roentgenologic features of the commonest reactions of bone to various agents. Diseases of bones are classified according to etiology but not to anatomy. Descriptive anatomy is omitted, to the advantage of the text. The interrelationship of etiology, symptoms, and clinical and roentgenologic findings with the underlying pathologic anatomy and physiology provides clear, continuous reading. Prognosis and therapy (conservative and operative) are mentioned only briefly because they are not in the scope of the book. The inclusion of some historical data at the beginning of the discussion of each disease and the latest experimental data or current theories at the end of discussion add to the color and completeness of the volume. Some lists of references at the ends of the chapters are rather short and almost all are made up exclusively of French and German articles, to the disadvantage of the American reader.

Osteitis caused by cocci, bacilli, fungi, and parasites is discussed. The genotypic osteopathies, chondrodysplasia, and malformations of single bones follow in the next chapter. The use of the term "genotypic" instead of "congenital" simplifies the matter for the reader. Under osteopathies due to intoxication by metals and metalloids, rare osseous lesions, such as those due to radium, beryllium, and cadmium, are described.

Osteopathies due to hormonal imbalance, vitamin deficiencies, diseases of the hematopoietic system, and renal diseases are dealt with expertly.

A chapter on posttraumatic osteopathies and another on aseptic necrosis of bone are followed by a consideration of osteopathies of unknown origin. Tumors of bone are described according to Lichtenstein's proposed classification. The use of the same term, namely, "benign giant-cell tumor," to signify a lesion of bone and, later, a different tumor of joints could be confusing to younger readers; it is better to designate the lesions in question as "giant-cell tumor" of bone and "pigmented villonodular synovitis." The chapters on arthritis and arthroses, especially those on rheumatoid, palindromic, and psoriatic arthritis, and ankylosing spondylarthritis, are excellent. Perhaps the potential dangers in the use of steroid agents for treatment are not sufficiently stressed.

In the third part of the book, the sections on the sciatic syndrome, differential diagnosis of a protruded intervertebral disc, the shoulder-hand syndrome, and cervical pain provide instructive reading.

The original schematic drawings and illustrations are selected purposefully and add to the completeness of the work. The book is heavy (8 pounds, or 3.6 kgm.) but the discomfort caused by this weight is well balanced by the simple style and by the concise, descriptive sentences. Readers with even moderate knowledge of French should have no difficulty in following the easy narrative flow of this useful book.

—*Alvina O. Sabanas.*

THE BOOK *Surgery of the Elbow*[3] by Frederick M. Smith fulfills a definite need in bringing together the many surgical conditions that are encountered in the elbow. The material is presented in a logical sequence and is written in a manner that is easily read.

The major part of this book concerns lesions which are the result of trauma. Much space is devoted to

[1] STANDARD VALUES IN NUTRITION AND METABOLISM. Being the second fascicle of a HANDBOOK OF BIOLOGICAL DATA. Edited by Errett C. Albritton, A.B., M.D. Prepared under the direction of the Committee on the Handbook of Biological Data. American Institute of Biological Sciences, The National Research Council. 380 pages. $6.50. Philadelphia and London: W. B. Saunders Co., 1954.

[2] MALADIES DES OS ET DES ARTICULATIONS. By Stanislas de Sèze and Antoine Ryckewaert. 1,218 pages, 391 illustrations. Paris: Éditions Médicales Flammarion, 1954.

[3] SURGERY OF THE ELBOW. By Frederick M. Smith, M.D. 340 pages, 153 illustrations. Springfield, Ill.: Charles C Thomas, 1954.

traumatic disabilities encountered in children. This is justified for a great deal of the clinical work is of this nature. The sections concerning epiphyseal injuries and various complications of fractures and injuries of soft tissues are very good. Much is gained by the fact that the book presents the views of a surgeon who has had a great deal of experience in surgery of the elbow, yet this necessarily limits the presentation of other approaches which have been found to be of much value.—*J. S. Speed.*

THE PURPOSE of *Biochemical Investigations; in Diagnosis and Treatment*[4] is to furnish a practical guide for the house staff of hospitals and also for practicing physicians. Biochemical determinations are becoming increasingly important in the management of patients in all branches of medicine. This book should help in the selection of tests for differential diagnosis in difficult problems as well as selection of tests that are necessary for the proper control of treatment. The book is written from a clinical viewpoint and does not have detailed description of laboratory methods. References are given for tests requiring the active participation of the clinician. At the end of each chapter there is a list of books and articles which can be used for further information on the subject discussed.

The book consists of 299 pages and includes chapters on disturbances of water and sodium metabolism, acid-base equilibrium, mineral metabolism, disturbances of protein and nitrogen metabolism, carbohydrate metabolism and diabetes mellitus, disorders of fat metabolism, diseases of the gastrointestinal tract, pancreas, liver, and biliary tract. There are also chapters on renal function, cerebrospinal fluid, endocrine glands, vitamins, and poisoning. At the end of the book there are detailed tables of normal values for determinations on blood, urine, and feces.

The author has accomplished the purpose of the book in a clear and simple discussion of the metabolism of the body and the results of biochemical determinations in relation to disease. He has pointed out the practical and important tests to use in different diseases. This book should be a great help to the senior medical student and the house staff of any hospital as well as to the practicing physician.—*Opal Hepler.*

THE PURPOSES SET FOR HIMSELF by the author of the monograph entitled *Hernia*[5] is to present briefly the common types of hernia, with particular emphasis on the anatomic defect characteristic of each. A single method of surgical repair, obviously the one he prefers, is described. These purposes are admirably fulfilled. The book is in atlas form and is featured by a series of excellent line drawings which were executed by Lucille Cassell Innis. These are accompanied by explanatory legends and a concise text.

The author's interest in the anatomy of hernia, and his particular concern with the transversus abdominis layer as the critical structure, are well known. The anatomic illustration which accompanies each hernia type is a posterior view of this musculoaponeurotic stratum. This view is unfamiliar to most readers either from other illustrations or from experiences at the operating table, and may offer some difficulty of orientation.

While the importance of this layer must be admitted, the complete disregard of the more superficial structures leaves the genesis of certain important types of hernia, such as the direct inguinal variety, inadequately explained. Also, as would be anticipated, the importance of Cooper's ligament in inguinofemoral hernioplasties is emphasized in this atlas.

This book is a valuable addition to the long list of monographs on hernia and is recommended for all who wish to add to their understanding of the fundamental anatomy of abdominal hernias, and of the methods for their repair.—*Leo M. Zimmerman.*

THE EXHAUSTIVE TREATISE *Cuarto congreso uruguayo de cirugia*[6] contains the entire transcript of the Fourth Uruguayan Congress on Surgery, held November 30 to December 5, 1953. The program of the meeting is presented in prologue, and the papers of the plenary session as well as those of the sectional meetings are transcribed in full along with discussions, questions, and answers. A more complete coverage could not be desired.

The first plenary session was devoted to the diagnosis and treatment of mammary tumors with special emphasis given to the various forms of cancer, whereas the second session discussed hepatic echinococcosis, and the third was concerned with peritoneal and subperitoneal drainage.

The sectional meetings contained an impressive array of topics covering salient features of current surgical thought in gynecology, urology, anesthesiology, orthopedics, neurosurgery, otorhinolaryngology, radiology, pediatrics, and plastic surgery.

Benign tumors of the stomach were discussed and a provocative paper on perineal prostatectomy made this difficult surgery appear easy and routine. The repair of tendons was masterfully depicted and the end result of the author's definitive surgery compared favorably with any reviewed in present day literature.

Surgery of the quality presented at the Fourth Uruguayan Congress is in the vanguard and cannot be confined by geographic boundaries.

—*Stephen A. Zieman.*

AN EXTENSIVE MONOGRAPH, *Peripheral Vascular Diseases*,[7] appeared in 1946 from the Mayo Clinic. This volume was reviewed in this Journal and it is interesting to compare this second, thoroughly revised edition with the first. While the new edition is 46 pages shorter and has lost 70 illustrations, it may be significant that

[4]BIOCHEMICAL INVESTIGATIONS; IN DIAGNOSIS AND TREATMENT. By John D. N. Nabarro, M.D., M.R.C.P. 299 pages, 5 illustrations. $6.00. Boston and Toronto: Little, Brown & Co., 1955.

[5]HERNIA; THE PATHOLOGIC ANATOMY OF THE MORE COMMON HERNIAS AND THEIR ANATOMIC REPAIR. By Chester B. McVay, M.D., Ph.D. 40 pages, 19 plates. $4.75. Springfield, Ill.: Charles C Thomas, 1954.

[6]CUARTO CONGRESO URUGUAYO DE CIRUGIA. November 30 to December 5, 1953. Sede: Agrupacion Universitaria del Uruguay. 971 pages, illustrated. Montevideo, Uruguay, 1954.

[7]PERIPHERAL VASCULAR DISEASES. By Edgar V. Allen, B.S., M.A., M.D., M.S. in Medicine, F.A.C.P., Nelson W. Barker, B.A., M.D., M.S. in Medicine, F.A.C.P., and Edgar A. Hines, Jr., B.S., M.S., M.D., M.S. in Medicine, F.A.C.P. With associates in the Mayo Clinic and Mayo Foundation. 2nd ed. 825 pages, 316 illustrations, 7 in color. $13.00. Philadelphia and London: W. B. Saunders Co., 1955.

surgical treatment has been given more space in line with recent developments.

The volume, its style of presentation, is obviously aimed at the general practitioner, giving him a fair and up-to-date estimate of the present trends of thought and clearly defining the attitude and practices of the Rochester group. The new chapters deal with such subjects as aortography, coarctation of the aorta, purpura, hypertensive ulcers of the leg, surgical treatment of aneurysms, and several others.

For the general surgeon who deals with peripheral vascular disease, this monograph represents a storehouse of information. Its style is informal, at the level of postgraduate instruction, and the printing and illustrations are excellent. The revision represents a vast improvement over the first edition and is the best single treatise on peripheral vascular disease.

—*G. de Takats.*

NUMEROUS THEORIES regarding the causative factors of new bone formation in bone transplants have been presented in the literature. None of them, however, has proved to be satisfactory. On the other hand, the process of healing and blending of bone transplants is quite well known. Most authors agree that reconstruction of bone tissue includes several different processes. The bone cells all die and must be replaced by living cells. Revitalization occurs whether through the bone-forming cells of normal bone tissue, through bone-forming cells from the soft tissues of the transplant, or by metaplasia of unspecific supportive tissues. Differentiation of these three factors is exceedingly difficult experimentally and impossible clinically. Therefore, much controversy exists regarding the actual value of different transplants. In previous experiments carried out with Maatz and Graf, the author of *Die Grundlagen der Transplantation von fremden Knochengewebe*[8] has been able to demonstrate the following facts: (1) Fresh autogenous transplants participate actively in the process, and at no time do they offer the slightest resistance to the developing structural changes. (2) In many instances a fresh homologous transplant behaves very similarly to an autogenous graft; in others, however, it does not show any active participation in the process. (3) Fresh heterologous transplants resist structural modifications much longer; at all times they prove to be inferior to homologous grafts. (4) Dead autogenous transplants inhibit, while dead heterologous transplants probably stimulate the reconstructive process. Homologous grafts were shown to act in both ways, presumably on account of proteinic differences between donor and receptor. (5) Under favorable conditions a bone transplant can be kept alive outside the body for approximately 2 weeks.

Two hundred seventy-six experiments were carried out in dogs, and 40 fresh homologous transplants were used. Although histologic differences were noticed, no essential difference could be regularly determined. In 236 other experiments, transplantation of dead bone grafts caused an inhibition of all positive and negative reactions.

Preservation of bone tissue always implies death of the tissue cells. Although many different methods of conservation have been advocated, never in the past have they ever been compared to each other. Comparative results of the eight commonest procedures were studied. Definite conclusions could be drawn regarding the reconstructive potentialities of cortical and cancellous bone respectively, and the possible effect of consanguinity between receptor and donor. Further tests were carried out in order to determine whether the defense mechanisms elicited in response to homologous grafts could be diminished by means of antihistaminic drugs.

The following conclusions could be drawn: (1) In all cases of longstanding conservation, no live bone tissue was left. Although such a graft may stimulate bone formation in the surrounding tissues, its own cells never take any active part in the reconstructive process. (2) Reactive mechanisms are comparatively less pronounced against preserved transplants than against fresh transplants of similar bone. (3) The best method of preservation was found to be the so-called deep-freezing method. By this, biologic values of bone tissue can be preserved for a very long, perhaps an unlimited period of time. (4) Preservation in indifferent solutions (Tyrode's solution with addition of serum; preserved blood) at refrigerator temperatures also provides a biologically satisfactory bone. Time of conservation, however, is limited on account of autolytic processes occurring in the preserving medium. (5) The biologic values of bone preserved in different solutions (cialit, equivalent to American merthiolate) were shown to be considerably decreased, at least in the first stage of the reconstructive process. (6) Inhibition of the reconstructive process is very marked for a period of weeks whenever macerated or boiled transplants have been used. (7) The structure of a transplant is of considerable importance. Cancellous bone, due to its greater surface, is much superior to cortical bone in regard to the duration of the reconstructive period. (8) Transplantation of consanguineous grafts does not influence more favorably the reconstructive process. (9) No stimulation of reconstruction could be elicited when different antihistaminic drugs were used in an effort to inhibit the resistance of the receptor's organism. Regarding the last two points, finer differences could not be displayed by the method used. They were so minimal in fact that they would be of no practical significance.

In addition to transplantation of bone tissue into soft tissues, the "spongiosa test" described by Maatz is considered to be the most practical method available for the determination and evaluation of the frequently concealed mechanisms taking place in the reconstructive process of bone tissue.

The author concludes that the use of foreign bone transplants in clinical practice rests upon the exact understanding of the first two points described. It is of great practical value to know that in many cases (fresh fractures, etc.) any material, although of little biologic value, will fulfill its purpose as a stimulant of bone formation, provided that it fulfills certain mechanical requirements. These cases should be considered as providing absolute indications for the use of foreign bone transplants, since under such circum-

[8]DIE GRUNDLAGEN DER TRANSPLANTATION VON FREMDEM KNOCHENGEWEBE. By Dr. Med. Wolfgang Lentz. With a foreword by Prof. Dr. R. Wanke. 111 pages, 69 illustrations. DM 18. $4.30. Stuttgart: Georg Thieme Verlag, 1955.

stances the active participation of fresh autogenous bone is not a requirement. In the treatment of other conditions (extra-articular arthrodeses, ordinary pseudarthrosis) only bone of high biologic quality should be used. A fresh autogenous graft will provide the best chances for a satisfactory reconstruction, although satisfactory results can also be expected at times from properly preserved bone. These cases actually provide limited indications for the use of foreign bone transplants. In all cases in which it is necessary to bridge a large defect that is present in the soft tissues, the use of foreign bone is contraindicated; only an autogenous graft will give successful results.

—*F. R. Schmidt.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Perinatal Mortality in New York City; Responsible Factors. A Study of 955 Deaths by the Subcommittee on Neonatal Mortality, Committee on Public Health Relations, the New York Academy of Medicine. Analyzed and reported by Schuyler G. Kohl, M.S., M.D., Dr.P.H. 112 pages. $2.50. Cambridge, Mass.: Published for The Commonwealth Fund by Harvard University Press, 1955.

The Mayo Clinic. By Lucy Wilder. Illustrated by Ruth Barney. 2nd ed. 69 pages, illustrated. $3.75. Springfield, Ill.: Charles C Thomas, 1955.

Erlebtes aus der Thoraxchirurgie. By Prof. Dr. Rudolf Nissen. 66 pages, 99 illustrations. DM 14.40. $3.40. Stuttgart: Georg Thieme Verlag, 1955.

Comment traiter les aménorrhées. By Albert Netter. 100 pages. Paris: Éditions Médicales Flammarion, 1955.

Casimir Funk; Pioneer in Vitamins and Hormones. By Benjamin Harrow. 209 pages, illustrated. $4.00. New York: Dodd, Mead & Co., 1955.

Gynaecology. By Douglas H. MacLeod, M.S.(Lond.), F.R.C.P.(Lond.), F.R.C.S.(Eng.), F.R.C.O.G., and Charles D. Read, M.B.(N.Z.), F.R.C.S.(Eng. & Ed.), F.R.A.C.S., F.R.C.O.G. Section on Anatomy by James Snyder, M.D., F.R.C.S. Section on Physiology and Endocrinology by Russell Fraser, M.D., F.R.C.P. 5th ed. 864 pages, with 551 illustrations including 27 in color. $16.00. Boston: Little, Brown & Co., 1955.

Bakteriologie und Serologie; Ausgewaehlte untersuchungsmethoden fuer das bakteriologische und serologische Laboratorium. By Dr. Lothar Hallmann. 2nd rev. ed. 850 pages, 273 illustrations. DM 58.50 $13.90. Stuttgart: Georg Thieme Verlag, 1955.

La transfusion intra-artérielle. By Louis Hollender and André Berner. Preface by Pr. A.-G. Weiss. 164 pages, 22 illustrations. 1.200 fr. Paris: Masson & Co., 1955.

Bone and Joint X-Ray Diagnosis. By Max Ritvo, M.D. 752 pages, 568 illustrations. $20.00. Philadelphia: Lea & Febiger, 1955.

Survey of Clinical Pediatrics. By Lawrence B. Slobody, M.D. 2nd ed. 502 pages. $9.50. New York, Toronto, London: McGraw-Hill Book Co., Inc., The Blakiston Division, 1955.

Essentials of Orthopaedics. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S. 2nd ed. 538 pages, 393 illustrations and 7 color plates. $10.00. Boston: Little, Brown & Co., 1955.

Breast Cancer and Its Diagnosis and Treatment. By Edward F. Lewison, B.S., M.D., F.A.C.S. 478 pages, 181 illustrations. $15.00. Baltimore: The Williams & Wilkins Co., 1955.

The Plasma Proteins in Pregnancy; a Clinical Interpretation. By Harold C. Mack, M.D. Foreword by Nicholson J. Eastman, M.D. 118 pages, 22 illustrations. $3.75. Springfield, Ill.: Charles C Thomas, 1955.

Obstetrics. By J. P. Greenhill, M.D. 11th ed. 1088 pages, 1170 illustrations, 144 in color. $14.00. Philadelphia and London: W. B. Saunders Co., 1955.

The Biologic Effects of Tobacco; with Emphasis on the Clinical and Experimental Aspects. Edited by Ernest L. Wynder, M.D. Foreword by Joseph Garland, M.D. 215 pages, 20 illustrations. $4.50. Boston and Toronto: Little, Brown & Co., 1955.

Sexual Hygiene and Pathology; a Manual for the Physician. By John F. Oliven, M.D. 462 pages. $10.00. Philadelphia and Montreal: J. B. Lippincott Co., 1955.

Rauber-Kopsch Lehrbuch und Atlas der Anatomie des Menschen. By Dr. Fr. Kopsch. Eingeweide, Nervensystem, Sinnesorgane. Vol. II. 768 pages, 782 illustrations. DM 64.50. $15.35. Stuttgart: Georg Thieme Verlag, 1955.

Midwifery. By ten teachers under the direction of Frederick W. Roques, M.D., M.Chir., F.R.C.S., F.R.C.O.G. Edited by Frederick W. Roques, John Beattie, and Joseph Wrigley. 9th ed. $7.00. Baltimore: The Williams & Wilkins Co.; London: Edward Arnold (Publishers) Ltd., 1955.

Die cervikalen Vertebral-Syndrome; Eine vorlaeufige Bilanz der Kliniker. Edited by F. Reischauer. 71 pages. DM 7.80. $1.85. Stuttgart: Georg Thieme Verlag, 1955.

Antenatal and Postnatal Care. By Francis J. Browne, M.D. (Aberd.), D.Sc., F.R.C.S.(Edin.), F.R.C.O.G., and J. C. McClure Browne, B.Sc., M.B., B.S., F.R.C.S. (Edin.), F.R.C.O.G. 8th ed. 672 pages, 94 illustrations. Boston: Little, Brown & Co.; London: J. & A. Churchill Ltd., 1955.

The Spine; a Radiological Text and Atlas. By Bernard S. Epstein, M.D. 539 pages, 721 illustrations on 331 figures. $16.50. Philadelphia: Lea & Febiger, 1955.

Lehrbuch der praktischen Orthopaedie. By Dozent Dr. Walther Aberle, Prof. Dr. Philipp Erlacher, Dr. Alexander Hartwich, Dr. Alfons Königswieser, and Prof. Dr. Oskar Stracker. 549 pages, illustrated. $24.50. Wien-Bonn: Wilhelm Maudrich, 1955.

Curso extraordinario de cancerologia para graduados, August 2–7, 1954. Directed by Prof. Dr. Abel N. Canonico. 344 pages, 4 illustrations. Buenos Aires: Ministerio de Educacion, Facultad de Ciencias Medicas, Universidad de Buenos Aires, 1955.

AMERICAN COLLEGE OF SURGEONS

ALFRED BLALOCK, Baltimore, *President*

WARREN H. COLE, Chicago, *President-Elect*

PRELIMINARY PLANS FOR THE 41st CLINICAL CONGRESS THE CONRAD HILTON HOTEL, CHICAGO, ILLINOIS OCTOBER 31 TO NOVEMBER 4, 1955

PLANS FOR THE 1955 CLINICAL CONGRESS in Chicago, October 31 through November 4, continue to expand, with every indication that this program will be the most useful ever held. More details will be unfolded here each month as the program develops, with the complete program scheduled to appear in the October issue.

Sessions in some of the surgical specialties will have great interest for all surgeons, and special attention is called to Friday's Joint Session in Urology (Topics, time, and moderators are listed, with collaborators to be announced in the next issue):

TUESDAY, 1:30–3 p.m.—Panel on Management of Undescended Testes. Moderator: NORRIS J. HECKEL, Chicago

WEDNESDAY, 3:30–5 p.m.—Panel on Management of Prostatic Hypertrophy. Moderator: VICTOR F. MARSHALL, New York

THURSDAY, 1:30–3 p.m.—Panel on Management of Renal Lithiasis. Moderator: CHARLES C. HIGGINS, Cleveland

FRIDAY, 1:30–3 p.m.—Panel on Evaluation of Supraradical Surgery in Malignant Disease of the Lower Abdomen and Pelvis. Moderator: EUGENE M. BRICKER, St. Louis. With collaborators from General Surgery, Gynecology, and Radiology

Gynecology and Obstetrics Panel Discussion Sessions

This year's program has been enlarged to meet the demand for inclusion of a larger number of sessions devoted to subjects in obstetrics. Topics, time, and moderators only are indicated here. Collaborators will be announced in the next issue:

MONDAY, 1:30–3 p.m.—Panel on The Place of the Dilatation and Curettage in Gynecology. Moderator: LEWIS C. SCHEFFEY, Philadelphia; 3:30–5 p.m.—Cesarean Section. Moderator: CURTIS TYRONE, New Orleans

TUESDAY, 1:30–3 p.m.—Conservation of Ovarian Tissue. Moderator: JOHN MCLEAN MORRIS, New Haven; 3:30–5 p.m.—Estimation of Pelvic Size. Moderator: M. EDWARD DAVIS, Chicago

WEDNESDAY, 1:30–3 p.m.—Blood Clotting Problems in Obstetrics. Moderator: DUNCAN E. REID, Boston; 3:30–5 p.m.—Studies in the Radiosensitivity of Tumors. Moderator: SAUL B. GUSBERG, New York

THURSDAY, 1:30–3 p.m.—Surgical Forum Reports in Gynecology and Obstetrics

FRIDAY, 1:30–3 p.m.—Hazards of Fetal Existence. Moderator: JOHN PARKS, Washington, D. C.; 3:30–5 p.m.—Care of Patient Under Radiation Therapy. Moderator: HERBERT E. SCHMITZ, Chicago

Neurologic Surgery Panel Discussion Sessions

THURSDAY, 9 a.m.—Symposium on Management of Facial Pain. Moderator: BRONSON S. RAY, New York; 10:30 a.m.—Symposium on Surgical Management of Upper Extremity Pain. Moderator: E. S. GURDJIAN, Detroit

Orthopedic Surgery Panel Discussion Sessions

FRIDAY, 9:30–10:30 a.m.—Fractures of the Lower End of the Radius and Fractures of the Carpal

Bones: Diagnosis, Treatment, Prognosis. Moderator: JESSE T. NICHOLSON, Philadelphia; 1:30–3 p.m.—Differential Diagnosis and Treatment of Neck, Shoulder, and Arm Pain. Moderator: JOSEPH A. FREIBERG, Cincinnati

Thoracic Surgery Panel Discussion Sessions

FRIDAY, 1:30–3 p.m.—Management of Emphysematous Blebs and Spontaneous Pneumothorax. Moderator to be announced; 3:15–4:45 p.m.—Recent Developments in Cardiac Surgery. Moderator: WILLIS J. POTTS, Chicago

Plastic Surgery Panel Discussion Sessions

FRIDAY, 9–10:30 a.m.—Tissue Banking and Skin Preservation. Moderator to be announced; 1:30–3 p.m.—Carcinoma of the Face, Mouth, Jaw and Neck. Moderator: WILLIAM F. MACFEE, New York

General Sessions

General sessions will begin promptly at 10 a.m. on Monday morning, with a panel discussion on Surgery of the Thyroid, with Richard B. Cattell the moderator. His collaborators include Thomas J. Anglem, B. Marden Black, and Howard A. Patterson.

A clinicopathology conference, with Edwin F. Hirsch the moderator, will be held at 1:30 p.m., followed by a panel discussion on Parenteral Therapy, to be moderated by Carl A. Moyer.

Carcinoma of the Breast will be discussed on Tuesday at 1:30 p.m., with Clarence E. Gardner, Jr., as moderator. The Symposium on Trauma, with Chairman R. Arnold Griswold, will follow. Final panel discussion on Tuesday will be on Surgery in Patients with Cardiac Disease, led by Charles G. Johnston.

Surgery and Anesthesia will be the topic for discussion on Wednesday at 1:30 p.m., with Frank Gerbode moderating. The Symposium on Cancer will follow at 2 p.m., led by Chairman Danely P. Slaughter. The final panel on Wednesday will be on Benign Lesions of the Pancreas, with John H. Mulholland as moderator, at 3:30 p.m.

Surgery of the Colon is the topic for Thursday's 1:30 p.m. session, with Claude F. Dixon the moderator. Collaborators include A. Stephens Graham, Jessie C. Gray, and Mr. T. McW. Millar of Edinburgh.

The distinguished Trauma Oration, a Clinical Congress tradition since 1929, will be given by Frank B. Berry, Assistant Secretary of Defense (Health and Medical), Washington, D. C. His subject, "Mass Casualties," is scheduled for 2 p.m. on Thursday.

"What's New In Surgery"—initiated with such success at the 1954 Congress—will be heard on Friday morning, from 9 to 12 noon, with Harris B. Shumacker, Jr. as Chairman.

Evening Sessions

Grayson L. Kirk, eminent President of Columbia University, will deliver the Martin Memorial Lecture on the opening evening of the Congress, at 8:30 p.m. On Friday evening, the Convocation evening, Dr. Warren H. Cole will give his Presidential Address, speaking on "Surgical Philosophy Old and New."

Otolaryngology and Ophthalmology

One evening session only in each specialty will be held, due to the meetings of the American Academy of Ophthalmology and Otolaryngology in Chicago prior to the Congress. Details will be announced shortly.

Postgraduate Courses

Courses will meet Monday through Thursday, with the exception of Obstetrics and Gynecology, which will meet Monday through Friday. All courses run from 8:30 to 11:30 a.m. Fee is $5.00 per course. Seating will be limited, so that early registration for the course of your choice is recommended. As an added convenience, your course ticket will be mailed to you in advance. Courses and chairmen are:

Preoperative and Postoperative Care. HENRY N. HARKINS, Seattle

Gastrointestinal Tract. JOHN D. STEWART, Buffalo

Diseases of the Liver, Biliary Tract, and Pancreas. ROBERT N. ZOLLINGER, Columbus

Cardiovascular Surgery. C. WALTON LILLEHEI, Minneapolis

Hand Injuries. MICHAEL L. MASON, Chicago

Obstetric and Gynecologic Surgical Care. JOHN I. BREWER, Chicago

Malignant Bone Tumors. MURRAY M. COPELAND, Washington, D. C.

Surgical Aspects of Pulmonary Disease. HERBERT C. MAIER, New York

Forum on Fundamental Surgical Problems

Sixteen Surgical Forum sessions will be held this year, with one or more sessions for five special fields of surgery. These meetings will be held Monday through Friday, mornings and afternoons. Harris B. Shumacker, Jr., is Chairman.

Color Television

Almost all the surgical specialties will be represented in the color television program originating from the University of Illinois College of Medicine Research and Education Hospital. A new Congress feature will be the panel discussion on each operation viewed, and, through two-way communication, the audience may ask questions of surgeons at the scene. More details on this program will be announced soon.

Ciné Clinics

A new plan will be followed in the Ciné Clinic program too, making this event even more valuable than it has been: there will be a discussion session after each film, with questions from the audience answered by the surgeon who made the film. Another major feature: several films on cancer of the large intestine will be shown, and discussed by a panel of experts.

Motion Pictures

Carefully selected films will be shown mornings and afternoons Monday through Friday. The choice of films represents the considered thinking of an important committee which has worked diligently to create the finest possible Congress film program. Fellows and their film assignments are as follows:

GUSTAF LINDSKOG—Consultant on Ciné Clinics
MICHAEL L. MASON—Plastic and Reconstruction
JAMES J. CALLAHAN—Orthopedics
JOHN W. HUFFMAN—Obstetrics and Gynecology
NORRIS J. HECKEL—Urology
RUDOLF J. NOER—Thoracic and Children's Surgery
B. MARDEN BLACK—Head and Neck
GEORGE CRILE—Surgery of the Esophagus
CHARLES PUESTOW—Surgery of the Stomach and Intestine
RICHARD B. CATTELL—Biliary Tract Surgery

The popular Motion Picture Symposium, scheduled for Wednesday evening, will feature "New or Unusual Problems in Surgery"— a series of short films personally narrated by the authors.

Advance Registration

An advance announcement containing necessary forms for Clinical Congress registration, hotel accommodations, postgraduate courses, and transportation information has been mailed to all Fellows. Non-Fellows may obtain these forms by writing to the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. Early return of these forms is urged for your convenience, since it assures that your badges will be waiting for you upon your arrival, that you have early choice at the postgraduate course of your selection, and that your hotel accommodations are in order.

Fees

No registration fee is charged Fellows if dues are paid to December 31, 1954. If dues are not paid, the fee is $20.00. No registration fee is charged Initiates. No registration fee is charged members of the Junior Candidate Group. No registration fee is charged Surgical Residents, provided a note of identification signed by the Chief of Surgery or Hospital Administrator accompanies the advance registration form. Non-Fellows will pay a $20.00 fee. Members of the Federal Services will pay a $10.00 fee. The Postgraduate Course fee is $5.00, payable by *everyone* taking a course.